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DIFFERENTIAL DIAGNOSIS OF TERMINAL GLOMERULONEPHRITIS AND MALIGNANT HYPERTENSION. I. RENAL ASPECTS *

By A. C. CORCORAN, M.D., and IRVINE H. PAGE, M.D., F.A.C.P.,
Indianapolis, Indiana

DIFFERENTIAL diagnosis in patients showing severe renal damage from chronic glomerulonephritis on the one hand, and malignant hypertension on the other has always been difficult. At this stage the two conditions have in common the clinical pattern of hypertension, loss of weight, anemia, so-called "albuminuric retinitis," depressed renal function, azotemia, proteinuria and increased organized urinary sediment. Indeed, at least cases 1 and 8 of Bright's original report and cases 1, 5 and 8 of his second paper in Osman's edition [1] seem to us instances of hypertension, essential or malignant rather than the characteristic syndrome, glomerulonephritis, which now most characteristically bears his venerated name.

We selected for study two groups of patients who had in common the evidences of disease noted above and who had not, at the time of first observation, progressed to uremia with its coma, acidosis and jactitation. We shall present with others in the succeeding reports of this series diagnostic criteria based on (*a*) the study of the heart and (*b*) of the general clinical course of this group. Criteria selected from the cardiac or anamnestic segments of the total pattern will be shown to permit the establishment of a correct diagnosis in most instances. The purpose of the present report is to direct attention to criteria for diagnosis derived from studies of renal function. We shall show that in certain cases the diagnosis may be confidently established from these alone.

Methods, Terminology, Their Evaluation. The methods of renal functional study used were (1) determination of plasma inulin and diodrast clearances and of maximum tubular secretory capacity for diodrast (T_{mD}),

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From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana.

(2) urea clearance, (3) determination of maximum urinary non-protein specific gravity, (4) proteinuria, and (5) counts of urinary sediment.

Clearances of diodrast and inulin and Tmd were determined during intravenous infusion of these substances in patients whose urine was collected by catheterization and bladder washing. The methods used are similar to those described by Smith, Goldring and Chasis.[2] Each of the values reported in this communication is the mean of three satisfactory periods of urine collection. The measurements of diodrast-iodine and inulin were made as described by Corcoran and Page.[3, 4]

Since these methods are not in general use and since also their evaluation is not settled, we append the following review of the significance we attach to them.

Inulin Clearance. Plasma inulin clearance is a satisfactory measure of glomerular filtration rate in normal animals and in man (Smith[5]). Neither our own experience nor a review of the literature gives any indication that this relationship fails in terminal Bright's disease or malignant hypertension with renal failure. Consequently, in this report we shall accept plasma inulin clearance as the equivalent of the rate at which water and substances dissolved in this water are filtered through the glomerular capillaries.

Diodrast Clearance. Diodrast, dissolved in plasma water and in small measure bound by plasma albumin (Smith and Smith[6]), distributes itself throughout the interstitial fluids of the body. Renal tubular cells, presumably of the proximal convoluted tubule, possess a mechanism which readily and efficiently transfers diodrast or a variety of similar substances from interstitial to tubular fluid, whence it is excreted, apparently without tubular reabsorption. In addition, a fraction (about 0.15) of the plasma diodrast is filtered through the glomeruli into tubular fluid. The combined effect of filtration and secretion is that the renal venous diodrast level is very low or, in other words, the renal extraction of diodrast (percentile arteriovenous difference) is nearly complete. This, at least, is the situation in dogs (White and Heinbecker,[7] Corcoran, Smith and Page[8]) and there are compelling reasons for supposing that the same is true in normal man (Smith[9]). The small residue of diodrast in the renal venous plasma is there in part because some of this plasma is constituted of blood which nourished non-excretory renal tissue; in part also because of the equilibrium which must obtain between venous capillaries and interstitial fluid (Corcoran and Page[10]). The net effect is that the removal of diodrast from the area of interstitial fluid which directly bounds actively secreting tubules is complete.

Plasma clearance is the volume of plasma whose content of a substance is equivalent to the amount of that substance (in this discussion, diodrast) which appears in one minute's urine. Where the proportion of a substance cleared from plasma is less than 100 per cent, then the plasma clearance is correspondingly less than total renal plasma flow. But, when, as in the case of diodrast, the excretory tissues virtually remove all of it, then plasma

clearance may be regarded as the close equivalent of effective renal plasma flow, using the word "effective" to indicate the perfusion of excretory tissue. This equivalence, proposed by Smith, Goldring and Chasis,[2] we adhere to for reasons stated above, neglecting, because of its small influence on clearance, the contribution to urinary diodrast made by diodrast removed from red blood cells.[7, 8]

The equivalence of plasma diodrast clearance and effective renal plasma flow, valid under normal conditions, must be examined for its significance in the diseases with which we are here concerned, and first, experimentally. In published (Corcoran and Page[11]) and unpublished observations on dogs with experimental renal hypertension, due either to compression of the renal artery by a clamp or to experimental perinephritis, we have not observed failure of diodrast extraction, or of the analogously excreted material, phenol red, in the absence of uremia or of renal necrosis. On the contrary, the extraction of these substances from plasma by the kidneys was maintained in spite of wide variations of renal plasma flow. The equivalence of diodrast clearance and effective renal plasma flow is therefore maintained in experimental renal hypertension, and the analogy may be drawn to malignant hypertension in human beings. In experimental glomerulonephritis (Fouts, Corcoran and Page[12]) phenol red extraction was observed to decrease in the presence of severe injury; but this change was associated with concurrent depression of inulin extraction, and we have concluded that, as regards the residually functioning nephrons, extraction was presumably well maintained. This observation also may be extended to glomerulonephritis in human beings.

The equivalence of plasma diodrast clearance with effective renal plasma flow is invalid in conditions of widespread tubular renal injury, such as is caused by uranium (Bobey, Longley, Dickes, Price and Hayman[13]) or tartrate (Nicholson, Urquhart and Selby[14]) where the capacity of renal tubules to secrete is depressed while these tubules retain their connection with functioning glomeruli. Nephrons such as these Smith[9] refers to as "impotent." Findley, Edwards, Clinton and White[15] have suggested that such tubules may occur widely in the kidneys in hypertension, that they would decrease diodrast extraction and result in a level of plasma diodrast clearance *less* than true effective renal plasma flow. Smith,[16] and Goldring, Chasis, Ranges and Smith,[17] starting from a similar premise as regards tubular injury, view it as most probable that diodrast will diffuse in renal interstitial fluid from an injured tubular boundary to an adjacent intact tubule, where it can be secreted. The net effect in this latter instance is a level of plasma diodrast clearance *greater* than true effective renal plasma flow. For this phenomenon as it occurs in conditions of tubular injury we (Corcoran, Taylor and Page[18]) have proposed the term "vicarious clearance." That this process occurs in essential hypertension has been suggested by Goldring, Chasis, Ranges, Bradley and Smith.[9, 19] Their evidence cannot here be

considered in detail; it suffices to note that (*a*) the phenomenon is not uniform, even in hypertensives showing renal injury and (*b*) as Smith [16] has indicated, the discrepancy introduced into the equivalence of plasma diodrast clearance and renal plasma flow is not very great. For these reasons, we regard plasma diodrast clearance as the equivalent of effective renal plasma flow in malignant hypertension.

As we have indicated, in experimental glomerulonephritis there is reason to suppose that diodrast clearance would in fact measure effective renal plasma flow. The renal structural changes of glomerulonephritis in human beings are characteristically quite opposite to the condition of intact glomerulus and injured tubule which vitiates the relationship of diodrast clearance and effective renal plasma flow in toxic nephrosis. Consequently, except for unusual circumstances indicated below, we accept plasma diodrast clearance as the equivalent of effective renal plasma flow in clinical glomerulonephritis.

Filtration Fraction. Having thus reviewed the facts which lead us to regard inulin clearance as a measure of glomerular filtration rate and plasma diodrast clearance as the equivalent of effective renal plasma flow in the two diseases with which we have to deal, it follows that, in these conditions, as in normal circumstances, the volume of filtrate formed per cubic centimeter of plasma flowing through glomeruli may be taken as glomerular filtrate/plasma flow or inulin/diodrast clearance. This value is known as "filtration fraction." The hydrostatic factors which determine the volume of filtrate formed per c.c. of effective renal plasma flow have been discussed by Lamport [20] with regard particularly to renal arteriolar resistance. Normally, these include the arterial pressure, the resistance of afferent and efferent glomerular arterioles, intrarenal and intracapsular pressure and the osmotic pressure of the plasma proteins. In disease, but not in health, the factor of plasma protein concentration may become a highly significant variable, for hypoproteinemia is common in terminal Bright's disease and, as we shall show, is not infrequent in malignant hypertension with renal failure. Hypoproteinemia, by lowering plasma osmotic pressure, decreases the resistance to filtration and thus would, other factors being equal, increase filtration fraction. We have, therefore, found it desirable to calculate from Lamport's [21] figures 1 and 2 a value we term, "Corrected Filtration Fraction," and abbreviate as $F^{S=7.0}$. By it, we mean the level which filtration fraction would reach, if, other factors being equal, the patient's serum protein pressure were normal (26.4 mm. Hg). This osmotic pressure is taken as that which corresponds to a serum total protein content (abbreviated as S) of 7.0 gm. per 100 c.c. with albumin/globulin ratio 2.2. The normal value of corrected filtration fraction equals that of filtration fraction in normal people; in disease, its deviations from this normal indicate the theoretical effectiveness of glomerular filtration as it would be with the variable of serum protein content removed. The comparison of corrected filtration fraction with the observed level of filtration fraction indicates the extent to which variations of serum

protein content have influenced the capacity of the glomeruli as filtering beds. A low level of this value indicates that either the hydrostatic pressure in the glomerular capillaries is low or that the capillaries are themselves in large measure impermeable to filtration. A high level of this function indicates increased intraglomerular hydrostatic pressure. The further significance of this concept in the interpretation of functional changes in renal disease we shall communicate elsewhere.

Unfortunately, as we shall show, this function is not calculable in all the patients with whom we deal, since in some it leads to a negative number. To include these latter in our data, while avoiding a concept such as that of negative filtration, we have calculated by Lamport's methods the apparent terminal glomerular serum osmotic pressure and determined the difference in mm. Hg between this value and normal serum osmotic pressure. This pressure difference, abbreviated as $DP_o^{S=7}$ indicates, when positive, the effective head of filtration pressure at normal level of proteinemia, and, when negative, indicates the extra pressure which would have to be applied to establish filtration at normal levels of proteinemia. The relation between positive values of this function and corrected filtration fraction is shown in figure 1, as obtained from Lamport's calculations.

Tubular Secretory Mass (Tm_D). The diodrast excreted by secretion in the urine is determined by finding the urinary minute excretion of diodrast and subtracting from this value the diodrast present in urine as the result of filtration. This value, expressed in milligrams of diodrast (determined as iodine) is known as T_D. As the amount of diodrast brought to tubular cells in the blood is increased, a point is reached at which the cellular transfer system is saturated. The amount excreted by secretion at this point rises to a maximum (Tm_D) which is not altered by increasing still further the plasma diodrast concentration.

Until the point of tubular saturation is reached, i.e., as long as T_D is less than Tm_D, the renal extraction of diodrast remains normally at a maximum, as does likewise the level of plasma diodrast clearance. When, in normal kidneys, the amount of diodrast brought to them for excretion (renal blood flow $\times$ blood diodrast content) is large enough to saturate the cells, Tm_D is reached, the tubules are uniformly saturated, their percentile extraction of diodrast from blood decreases and clearance is therefore depressed. The measurement of Tm_D made in such circumstances is a measurement of one aspect of tubular functional capacity, viz., secretion. But, since the capacity to secrete must be considered uniformly distributed in the cells specialized to this function in every nephron, it follows that this measurement of maximum secretory activity is a measure of functioning tubular mass. The principle of measurement is that of counting the cars of a railroad in terms of the coal they can carry.

The high blood levels of diodrast necessary to saturate the tubules of normal kidneys do not ordinarily alter the rate of glomerular filtration.

Inulin clearance is, therefore constant and, diodrast clearance being depressed, the filtration fraction (inulin/diodrast clearance ratio) rises.

Were the kidney to be more severely injured in some large areas than in others, the damaged areas, impotent as regards secretion, would saturate when the diodrast "load" (amount presented to the cells for secretion per minute) was yet small, while in the better preserved areas of structure saturation would not yet be accomplished. Titration of secretory capacity by slowly increasing plasma diodrast concentration in normal patients and in some patients with hypertension has shown that such inequality of tubular activity is of minor degree (Smith [9]). That large variations in the degrees of focal tubular saturation occur in terminal glomerulonephritis is indicated by observations made in patients Nos. 5, 8 and 10 of this group. In these, as we shall show, plasma diodrast clearance was depressed and filtration fraction thereby increased at a ratio of T_D/Tm_D of about 0.3. We interpret this as signifying that certain tubular areas, presumably the most damaged, were fully saturated as regards secretory capacity at a time when two-thirds of the kidneys' capacity for secretion remained still unsaturated. This gross inequality of tubular secretory capacity we provisionally term "Focal Tubular Saturation." The explanation for its presence seems to be (1) the presence of tubular areas whose small residue of secretory capacity is saturated at even low renal loads of diodrast and (b) around which fibrosis prevents the escape of the diodrast in interstitial fluid to other relatively intact tubules.

Urea Clearance. The normal significance of urea clearance and its clinical value in Bright's disease have been reviewed in the monograph by Van Slyke and co-workers [22] and widely elsewhere. We need only here note that urea is normally excreted as the result of filtration and subsequent partial reabsorption. Under normal conditions and at levels of urine flow customary during the measurement of maximum urea clearance (C_m) the proportion of urea reabsorbed is relatively constant at about 50 per cent. The significant physiological variable in urea clearance is therefore the rate of glomerular filtration. Abnormally, in advanced Bright's disease, the reabsorption of urea may be somewhat decreased (Chasis and Smith [23]) but the effect is not usually a large one in the stage with which we deal here and the general parallelism of urea clearance and glomerular filtration rate is well maintained.*

Concentration Test. Ever since urinalysis passed from the phase of urinoscopy, the power of the kidneys to form urine of high specific gravity

* For many of the determinations of urea clearance and serum protein recorded in this report we are indebted to Dr. O. M. Helmer of this laboratory. We wish to acknowledge the technical assistance of Mr. Ora Harvey in these analyses. In every instance urea clearance was determined as the clearance of urea + urinary ammonia. The methods used by Dr. Helmer were, for urea determination, the urease aeration-titration of Van Slyke and Cullen and, for protein determination, micro-Kjeldahl digestion and Nessler colorimetry. The other determinations were, in the case of urea, made by the manometric hypobromite method of Van Slyke and Kugel and, in the case of protein, by biuret colorimetry. The change in methods does not involve any change in the data.

has been one of the simplest demonstrations of normal renal function. Practiced under controlled conditions, as is obtained in the Addis [24] or similar tests, the measurement provides a semi-quantitative index of renal injury. Its significance in Bright's disease has been reviewed by Alving and Van Slyke [25] and, with regard to hypertension, briefly by Corcoran and Page.[26] It will suffice here to observe that (1) urinary non-protein maximum specific gravity does not decrease progressively after it has reached a level near 1.010, although (Hayman, Martin and Miller [27]) the number of functioning nephrons continues to decrease. This apparent paradox is satisfactorily explained by Newburgh [28] in terms of the renal osmotic work. (2) In hypertension there is a general parallelism of concentrating power and Tm_D; concentrating power tends to be proportional to Tm_D and inversely proportional to some function of filtration rate.[26] This relationship in hypertension and Bright's disease will be the subject of a later communication.

Results

The observations of renal function and calculations made from them are summarized in tables 1, 2 and 3.

1. Differentiation of Malignant Hypertension with Renal Failure and Terminal Bright's Disease: Data of table 1. For convenience in presentation, we have calculated together with the data from the individual cases the means of the data from the patients in each group. We shall consider first the broad points of difference indicated by these means.

The nearly equal levels of renal blood flow (HD) and plasma diodrast clearance (DC) in the two groups accord with our impression that the clinical status of the patients in the two groups were comparable. A difference appears first in the levels of plasma inulin clearance (IC), the mean in terminal glomerulonephritis being nearly half that of the malignant hypertensives with renal failure. The higher inulin clearance in the hypertensives with nearly equal rates of plasma diodrast clearance results in a high filtration fraction (FF) in patients of this group. The mean filtration fraction recorded in Bright's disease is within the normal range (0.19 ± 0.024),[9]

Another wide difference is shown in the mean levels of tubular secretory capacity (Tm_D) which, in terminal glomerulonephritis, is less than half the value found in malignant hypertension. The higher level of Tm_D in the hypertensives with a rate of effective renal blood flow approximating that of glomerulonephritis results in a low mean value for the rate of effective renal blood flow per unit of functioning tubular mass (HD/Tm_D). In these malignant hypertensives, the residual tubular mass is thus shown to be definitely ischemic, while it is, if anything, hyperemic in terminal glomerulonephritis. That the renal ischemia present in the malignant hypertensives is due to increased renal vascular resistance greater than that in glomerulonephritis is emphasized by the higher level of arterial pressure in the hypertensives.

The expected low values of serum total protein and albumin content were found in patients suffering from glomerulonephritis; not as generally recognized is the frequent (five out of 10) occurrence of hypoproteinemia in malignant hypertension with renal failure. Similarly, the low hematocrit level in Bright's disease reflects the anemia characteristic of this condition in its terminal phase; that the hematocrit index should be nearly as low in malignant hypertension with renal failure was unexpected. The slightly lower hematocrit index of the nephritics resulted only in a somewhat lower level of effective renal blood flow for an equivalent rate of renal plasma flow;

TABLE I

Measurements of Renal Function in Terminal Bright's Disease and in Malignant Hypertension with Renal Failure

No.	Init.	HD	DC	IC	FF	Tm_D mg. D-I per min.	HD/Tm_D c.c. per min.	T.P.	Alb.	Hem. per cent	Pm. mm. Hg	DP_0S^{-7}
		c.c. per 1.73 sq. m. per min.						gm. per 100 c.c.				
A. Terminal Bright's Disease												
1	Fi.	191	130	22.2	0.17	9.2	20.7	4.6	3.2	32	154	−7.12
2	Mi.	138	92	17.6	0.19	7.15	19.3	5.5	3.8	34	155	−1.22
3	We.	70.3	50.6	13.4	0.26	2.68	26.7	6.4	3.7	29	141	4.58
4	Wi.	80.3	53.8	14.2	0.26	2.2	36.5	4.6	3.0	34	114	−6.53
5	Hu.	(31.1)	(23)	11.4	(0.5)	2.1		5.8	3.7	27	141	
6	Hi.	49.6	38.3	5.4	0.14	1.7	29.2	6.9	4.8	23	149	6.86
7	Sm.	25.1	17.3	4.5	0.26	0.8	31.2	4.3	1.5	32	147	−13.7
8	Ha.	(12.6)	(10)	3.9	(0.4)	0.6		6.1	4.0	20	157	
9	Co.	40.2	32.2	8.9	0.28	0.437	92	5.5	3.9	20	150	5.12
10	Fr.	(9.8)	(8.0)	3.1	(0.4)	0.32		5.7	3.8	18	124	
Mean*		85	59	12.3	0.22	3.45	36.5	5.5	3.5	27	143	−1.7
B. Malignant Hypertension with Renal Failure												
1	Ed.	163	116	28.3	0.28	11.27	14.96	6.7	4.2	29	189	13.8
2	Gr.	165	117	34.6	0.30	10.9	15.13	7.8	4.5	29	182	22.63
3	La.	82	47	18.5	0.39	8.62	9.4	5.6	3.7	42	162	14.88
4	Ho.	136	88	29.3	0.33	8.6	15.9	7.1	4.6	35	159	17.11
5	Mk.	109	73	20.3	0.28	8.1	13.4	6.4	4.1	33	159	10.16
6	Co.	98	60	23.4	0.40	7.8	12.6	5.7	3.8	39	163	17.15
7	Ar.	121	85	23	0.27	7.6	15.96	4.8	3.4	30	176	1.66
8	Re.	66.7	44.7	14	0.30	7.05	9.5	7.0	4.3	33	189	17.33
9	Ch.	75	50	15	0.29	5.9	12.7	5.5	2.9	33	213	−1.42
10	He.	88	56	16	0.29	4.5	19.6	5.5	4.5	36	180	11.28
Mean		110	74	22.2	0.31	8.0	13.9	6.2	4.0	33	179	+12.50

Renal function in terminal glomerulonephritis and malignant hypertension with renal failure, arranged in order of descending values of Tm_D per 1.73 square meters of body surface. Init.: initial letters of patient's surname; HD, effective renal blood flow; DC, plasma diodrast clearance; IC, plasma inulin clearance; FF, filtration fraction; Tm_D, maximum tubular secretory capacity for diodrast, mg. diodrast-iodine per minute. HD/Tm_D, effective renal blood flow per unit of Tm_D; T.P., serum total protein; Alb., serum albumin, gm. per 100 c.c.; Hem., hematocrit index, per cent; Pm., mean of systolic and diastolic arterial pressure. DP_0S^{-7} is the difference in mm. Hg between presumptive terminal osmotic pressure of patient's serum in glomeruli and normal serum osmotic pressure when S, i.e., serum total protein of albumin/globulin ratio 2.2, equals 7.0 gm. per 100 c.c.

TABLE II

Demonstration of Focal Tubular Saturation in Terminal Glomerulonephritis

No.	In.	Plasma Diodrast-Iodine mg. per 100 c.c.	Plasma Diodrast Clearance c.c. per min.	T_D (Tm_D) mg. D-I per min.	Filtration Fraction	HD/Tm_D c.c. per min.	T_D/Tm_D
5	Hu.	4.0	23	0.5	0.5	14.7	0.24
		26.0	18.4	(2.1)			(1.0)
6	Ha.	2·6	10	0.2	0.4	21	0.33
		25.0	5.7	(0.6)			(1.0)
10	Fr.	1.8	8.0	0.1	0.4	30.5	0.26
		4.5	7.1	0.21			0.55
		16.0	3.1	(0.38)			(1.0)

No. and In. as in table 1. Each value shown is the mean of those observed during three periods of urine collection. The high initial values of Filtration Fraction and low relative levels of diodrast clearance and HD/Tm_D indicate that renal diodrast extraction was depressed at the lowest level of plasma diodrast concentration observed in each case. Since, at this time, the amount of diodrast secreted (T_D) was less than the maximum (Tm_D) (the latter indicated in brackets under its heading) the conclusion is drawn that in focal areas tubules were saturated while others were not.

this as we have seen, is countered in a degree by the high rates of effective renal blood flow per unit of residually functioning tissue in these patients.

The effects of the differences in serum protein level are much more significant than those due to anemia. They are reflected in the values obtained for Corrected Filtration Fraction and its equivalent $DP_o^{S=7}$. In four of seven nephritics and one of 10 hypertensives, it appears that filtration would have ceased had serum protein been normal. Averaging the pressure differences algebraically, a negative value is obtained from the nephritics, indicating that filtration would not have occurred in the group had there not been hypoproteinemia. A positive value, at about the normal level, is obtained from the mean of the levels in the hypertensives.

To summarize these differences between the means observed in the two conditions, while also restating them in terms of their probable physiological equivalents, we note that (1) the rates of effective renal blood and plasma flow are nearly equal in patients with terminal Bright's disease and those with malignant hypertension and renal failure; the means are somewhat lower in the nephritics because no patient with malignant hypertension was found with effective renal plasma flow lower than 40 c.c. per minute whereas three such occurred among the terminal nephritics. (2) The rate of glomerular filtration is much lower among the nephritics; it was less than 15 c.c. per minute in eight of the nephritics and in only one of the hypertensives. (3) The coincidence of a lower filtration rate and nearly equal rate of effective renal plasma flow in the nephritic group results in their maintaining a mean level of filtration fraction lower than that of the hypertensives, i.e., the nephritics' tubules are presented with less glomerular filtrate than are those of the hypertensives. However, whereas the mean level of filtration frac-

TABLE III

Comparison of Generally Available Methods of Measuring Renal Function in Terminal Glomerulonephritis and Malignant Hypertension with Renal Failure

No.	Init.	Urea Clearance per cent of normal	Blood Urea N mg. per 100 c.c.	Proteinuria gm. per 24 hours	Maximum Specific Gravity	Urinary R.B.C.	Sediment Casts
						1000's per 24 hrs.	
A. Terminal Glomerulonephritis							
1	Fi.	11.6	38.6	2.5	1.014	330	27
2	Mi.	13.5	31.6	3.8		189	0.0
3	We.	11.3	42.8	10.6	1.009	197	0.0
4	Wi.	9.4	57.6	8.0	1.015	296	0.0
5	Hu.			4.9			
6	Hi.	4.9	80.5	7.1	1.017	367	20
7	Sm.			12.5	1.009		
8	Ha.	4.35	133	0.04	1.0095	1690	0.4
9	Co.	9.8	87	15.9	1.0125	880	10.4
10	Fr	5.1	133	2.5	1.010	1350	5.4
Mean		8.74	75.5	6.78	1.012	662	7.9
B. Malignant Hypertension							
1	Ed.	23.7	26.8	2.8	1.0145	2000+	1.1
2	Gr.	23.0	19.1	1.7		435	94.5
3	La.		21.2	0.2		930	1.1
4	Ho.			1.7	1.014	267	20.4
5	McK.	26.1	35	4.4	1.015	280	26.6
6	Coo.	31.6	39.7	1.5	1.014	340	37.5
7	Ar.	26.1	36.5	1.7	1.014	275	2.3
8	Re.	17.5	25.6	3.8	1.012	380	8.0
9	Ch.		58.5	1.4	1.012	300	10.5
10	He.	17.6	35.7	1·5	1.011	350	4.3
Mean		23.65	33.1	2.07	1.013	605	20.6

Comparison of urea clearance, blood urea nitrogen concentration, maximum urinary non-protein specific gravity, proteinuria and sediment counts of red blood cells (R.B.C.) and casts in patients suffering from terminal glomerulonephritis and those suffering from malignant hypertension. The order of listing is the same as in tables 1 and 2. Where data were not available or were obtained at such a time that they are not comparable with data presented in the preceding tables, they are omitted.

tion is higher than the normal among the hypertensives, it is within the normal range among the nephritics. (4) Renal ischemia, evidenced by a diminished rate of effective renal blood flow per unit of tubular secretory tissue (normal 23.86 ± 3.93 c.c. per minute, by calculation from Smith [9]) is present in nine of 10 malignant hypertensives, where the mean less twice standard deviation is taken as the lower limit of normal. Such an ischemia did not occur among the nephritics, whose values for this function were either normal, in the upper range of normal or, in one instance, about 400 per cent of normal. Comparison of the rates of effective renal blood flow with the corresponding levels of arterial pressure indicates that renal ischemia among hypertensives is due to increased renal resistance; otherwise their higher

levels of arterial pressure would have increased rather than decreased renal blood flow. (5) The anemia of terminal glomerulonephritis, as measured by hematocrit index, somewhat exceeds that of malignant hypertension with renal failure; none of the hypertensives showed a value equal to or less than the mean of 27 per cent found in the nephritics; four of the cases of glomerulonephritis yielded values less than this mean. (6) The hypoproteinemia of terminal glomerulonephritis and that often found in malignant hypertension in renal failure greatly alter the significance which may be attached to filtration fraction in these circumstances as compared with that attributed to this function in normal people. When allowance is made for this variable by the calculation of corrected filtration fraction (F_7) or $DP_o^{S=7}$, filtration would, in theory, cease in three of seven nephritics at levels of plasma protein content osmotically less than the normal, here taken as 7 gm. per 100 c.c. In contrast, only one of the hypertensive group would, in theory, have ceased filtering at a normal level of plasma osmotic pressure. It can be calculated that the average rate of glomerular filtration in the group would, in this concept, have been reduced from its actual value of 22 only to about 10 c.c. per minute.

II. Focal Tubular Saturation in Terminal Glomerulonephritis. We have described under the section on evaluation of the methods the possible occurrence of a state in which certain tubular areas, themselves severely injured and surrounded by fibrous tissue, would become saturated with diodrast and thus fail further to secrete it at a time when the secretory capacity of areas less severely injured was not yet exceeded. Restated, the concept demands that evidence be obtained of decreased renal extraction of diodrast from blood at levels of secretory rate (T_D) less than the maximum (Tm_D) and when the amount of diodrast brought to the kidney in the blood is also less than Tm_D. Decrease in diodrast extraction would be signified, apart from direct measurement, by low levels of diodrast clearance (or apparent effective renal blood flow) and high levels of filtration fraction, both out of proportion to values observed in the same patient at lower plasma diodrast concentrations or found in other patients similarly diseased. In table 2 we present data from three patients of the nephritic group in whom one or both of these conditions are fulfilled at low plasma concentrations of diodrast and at levels of diodrast secretion (T_D) equal to about one third or less of the maximum (Tm_D).

These observations were made incidentally during the proposed determination of plasma diodrast clearance in these patients. Direct titration of the actual inequality of tubular secretory activity by the methods of Smith [9] was not attempted, nor do the data permit its calculation, for in none of these was true maximum plasma diodrast clearance determinable. Nevertheless, the evidence indicates clearly the occurrence of Focal Tubular Saturation. Since these findings were made in terminal glomerulonephritics and have not been observed in any of our hypertensive patients, it seems

that the phenomenon of a wide inequality of tubular secretory activity may be one of the characteristics of advanced glomerulonephritis. In such patients no estimation of renal blood flow or filtration is possible by present methods.

III. Differentiation by Generally Available Means: Data of table 3. In table 3 we summarize observations of renal function based on urea clearance, blood urea nitrogen content, maximum urinary non-protein specific gravity, proteinuria and counts of the urinary sediment.

The difference between the two groups found in regard to glomerular filtration rate (inulin clearance) is repeated in the levels of urea clearance, the mean of which in terminal glomerulonephritics is less than half the mean rate in malignant hypertension with renal failure. None of the hypertensives showed a value equal to or less than the mean of 8.7 c.c. per cent of normal found in the nephritics. As would be expected from the lower level of urea clearance, blood urea nitrogen content is much higher among the nephritics. Another difference appears in the rate of proteinuria, which is more than twice as great in nephritics as compared to the hypertensives of our group. None of the hypertensives exhibited proteinuria equal or greater than the mean of nearly 7 gm. per 24 hours found in the nephritics; however, the overlapping lower values of some patients in both groups and the nearly normal rate (0.04 gm. per 24 hours) in one nephritic indicate that this measurement is not diagnostic in the lower ranges.

No differentiation could be made from the values of maximum urinary non-protein specific gravity, nor from the counts of red blood cells or of white and epithelial cells in urinary sediment, the latter determination not being included in the tabulation. The mean rate of cylindruria was significantly higher in the hypertensive groups, but the means of both groups were widely overlapped in certain cases.

Discussion

The arguments on which depend the interpretation of our data have been presented above in our "Evaluation of Methods." We need therefore here concern ourselves only with the clinical significance of the data and the problems they solve or suggest in clinical physiology.

Mansfield, Mallory and Ellis,[29] in a review of the differential diagnosis of Bright's disease, indicate that much confusion exists about the term "malignant hypertension," as did Page,[30] in an earlier study of this question. We use it in the sense defined by Keith, Wagener and Kernohan,[30] i.e., as a syndrome of severe hypertension of unknown origin, characterized by retinal hemorrhages, exudates and papilledema and progressing rapidly to a fatal outcome. The term, terminal glomerulonephritis, as we have used it requires no definition, at least, not as a clinical syndrome.[22] Stated in an older terminology, the demonstration proposed in this and the succeeding papers of this series is the distinction between patients who exhibit "albu-

minuric retinitis" and suffer from renal failure and who, at the time of observation, have not progressed to uremia. To make this distinction is not an academic problem of "deadhouse" interest, but, rather, clinically possible and important. Its importance, apart from etiological and functional connotations, lies in the time of survival of the patients in each group from the date at which observations were begun. This, in our malignant hypertensives, was 6.3 weeks and, in the glomerulonephritics, 6.4 + months, the plus sign (+) indicating that, at the time of writing, one terminal glomerulonephritic (No. 4, Wi.) is alive after 12 months.

The ability of the nephritic patient to tolerate severe renal injury and still survive for long periods as compared with malignant hypertensives whose renal function is, on the whole, much less affected, suggests that factors other than renal failure are the coöperating causes of death in malignant hypertension. These factors may be grouped together as expressions of a more severe arterial and arteriolar disease, as will be shown in the second paper of this series. This fact points to the advisability of dropping the term "malignant nephrosclerosis," with its connotation of a localized or primary lesion of the kidneys, even in patients such as our malignant hypertensives with renal failure to whom it would seem specially to apply. To retain it, one would have to justify the terminology of "coronarioarteriosclerosis, benign or malignant," and "cerebroarteriosclerosis, benign or malignant," in malignant hypertensives whose symptoms are respectively cardiac or cerebral in origin.

The significant means by which this distinction can be made by study of renal function are summarized in table 4. Taking the nine points there presented, diagnosis can be made cumulatively and by exclusion in all but one (No. 10) of the malignant hypertensives and in all but one (No. 2) of the glomerulonephritics. In both the exceptional patients, as we shall show in the studies which follow, the diagnosis can be established by studies other than renal.

The usefulness of each of these diagnostic criteria is indicated in table 4 by scoring their application to the two groups of patients studied. Among the generally available means of study, urea clearance and proteinuria are shown to be of positive value in the diagnosis of terminal glomerulonephritis. Of the methods of study which depend on the excretion of diodrast and inulin, the determinations of tubular secretory capacity, inulin clearance and effective renal blood flow per unit of residual secretory capacity are the most useful in glomerulonephritis; effective renal blood flow, corrected filtration fraction and observed filtration fraction have their application in the diagnosis of malignant hypertension with renal failure. The significance of focal tubular saturation in critical diagnosis, although included in the tabulation, remains to be demonstrated in a larger series.

In the classical monograph on Bright's disease [12] by Van Slyke and his co-workers of which this report represents in fact the reëxamination of a

segment, structural changes were the basis of their analysis of the functional concepts then introduced, notably that of clearance. Indeed, Addis and Oliver [32] have pointed out that no author, treating of this topic, has neglected to correlate the clinical and functional findings with the anatomical changes found at autopsy, nor do we propose to overlook this point of view in a subsequent study. However, because it is the point of this paper that the diagnosis can and should be established by functional means before autopsy, we can only note the general points of correlation. Among the glomerulo-

TABLE IV

Application of Tests of Renal Function as Means of Diagnosis in Terminal Glomerulonephritis and Malignant Hypertension with Renal Failure

No.	Test	Application	
		Terminal Glomerulonephritis	Malignant Hypertension with Renal Failure
1	Diodrast clearance	if less than 40 c.c. per min. (3)	must be more than 40 c.c. per min. (0)
2	Inulin clearance	if less than 12 c.c. per min. (6)	must be more than 12 c.c. per min. (0)
3	Urea clearance	if less than 10 c.c. per min. (5)	must be more than 10 per cent of nor- (0) [mal
4	Filtration fraction	if less than 0.15 c.c. per min. (1)	if more than 0.30 c.c. per min. (7)
5	Tubular secretory capacity (Tm_D)	if less than 4.0 mg. per min. (8)	must be more than 4.0 mg. per min. (0)
6	Effective renal blood flow (HD/Tm_D)	if more than 25 c.c. per min. (5)	if less than 18 c.c. per min. (9)
7	Difference P_a^{S-7}	if less than − 4 mm. Hg (5)	if more than 10 mm. Hg (8)
8	Focal tubular saturation	may be characteristic (3)	not observed as gross phenomenon (0)
9	Proteinuria	if more than 7.0 gm. per 24 hrs. (4)	must be less than 7.0 gm. per 24 hrs. (0)

Application of tests of renal function to differential diagnosis. The values stated as limiting the diagnoses vary slightly from the data of tables 1 and 2 in the direction of increasing their significance. Although diagnosis is in any case cumulative, it is probable when data fall into the category, "if less than . . ."; it is excluded when the values observed are less than indicated under the category, "if more than. . . ." Diagnosis is made by concurrence of positive findings. The numerals bracketed in relation to each test under the two diseases studied indicate the frequency of the occurrence of each finding as a useful criterion of diagnosis.

nephritics our data indicate a more or less characteristic depression of the rate of glomerular filtration and of tubular secretory capacity as compared to patients suffering from malignant hypertension with renal failure. These characteristics of the nephritic accord with the smaller, and more fibrous kidneys with greater parenchymal loss and glomerular intra- and extra-capillary disease found in kidneys of such patients. The high values of observed filtration fraction in malignant hypertension, the presence of renal ischemia and severe hypertension, would seem to agree with the concept (Goldring, Ranges, Chasis and Smith [17]) that such patients have a great deal

of renal vasoconstriction, whose resistance more than counters the increase of arterial pressure and thus reduces renal blood flow, and that the locus of this constriction is principally in the glomerular efferent arterioles. That this is indeed the case has been difficult to reconcile with the hyperplastic and necrotizing changes of the afferent arterioles characteristic of patients with malignant hypertension. This paradox seems to us to be reconciled by our finding that values of corrected filtration fraction are very low in two cases of the group and within the normal range in four. In other words, in spite of the great increase of systemic arterial pressure, the hydrostatic pressure within the glomerular capillaries would have been insufficient to maintain a filtration from the glomerular plasma in one patient and barely so in another had the plasma protein content been normal, and, in another four, hydrostatic pressure was not abnormally increased. We and others have reviewed evidences which point to the uniform presence of efferent arteriolar constriction in arterial hypertension. We do not believe that it was absent in those patients whose levels of corrected filtration fraction do not point to its presence, but rather, we suggest that the degree of afferent arteriolar sclerosis had in these been so great as to reduce intraglomerular hydrostatic pressure to normal or subnormal levels in spite of the separate activities of systemic hypertension and efferent constriction which tend to raise it. The functional data are thus shown to be altogether consistent with anatomical findings. Even the demonstration of focal tubular saturation in cases of glomerulonephritis, with its suggestion of the presence of nephrons largely deficient in secretory capacity, and removed from other healthier or hyperplastic nephrons by boundaries of fibrous tissue through which interstitial fluid does not move rapidly, is altogether consistent with the anatomical pattern of this disease, as demonstrated by Oliver.[33] This inequality of tubular activity, although to be expected in minor degree in malignant hypertension with renal failure, would not be as characteristic of a disease in which the death of nephrons presumably follows rapidly on the obstruction of afferent arterioles, rather than slowly as glomerular capillaries are thickened, while still canalized and eventually obliterated. The high levels of apparent renal blood flow per unit of residual tubular tissue found in glomerulonephritis may also be consistent with the glomerular, rather than pre-glomerular character of the disease. A high rate of blood flow through residual tubular tissue might well follow the slow obliteration of glomeruli, with the possibility of formation of pre-glomerular afferent arteriolar shunts (Ludwig's arteriole) of lower vascular resistance than the combined resistances of constricted afferent and efferent arterioles, whereas, because of low hydrostatic pressure, such shunts would have little stimulus to open in the course of necrotizing and hyperplastic afferent arterioles. Alternatively, the apparent high rate of tubular perfusion in glomerulonephritis may well be a reflection of "vicarious clearance," i.e., excretion of diodrast by intact or hyperplastic tubules when it cannot be excreted by adjacent tubules

deficient in secretion. In any case, the reconciliation of functional and structural findings in the aspects of Bright's disease with which we here deal seems to us to have been made.

Since it is the subject of a separate communication, we shall here only note in passing that the values of corrected filtration fraction observed in four of the glomerulonephritics and one of the patients with malignant hypertension indicate that, with similar setting of blood pressure and arterioles, glomerular filtration would either have ceased or have been almost absent, had these patients not also been hypoproteinemic. As regards the state of the vascular system and the possibility of its being adjusted to maintain filtration had plasma proteins been normal, we note that hypertension was present and severe in both groups, that it is very likely that the glomerular efferent arterioles were constricted in these patients also, and that the afferent arterioles were also arteriolosclerotic in both, so that adjustment to increase filtration by increasing pressure, constricting efferent or dilating afferent would have been difficult or impossible. Hypoproteinemia was, therefore, life-saving in the patients in whom it was present. We are thus led to the view that hypoproteinemia in renal disease is teleologically homeostatic, and that the stimulus which provokes it is a relative deficiency of glomerular filtrate in the residually intact tubular tissue.

Summary

The distinction between patients who show renal failure which has not progressed to uremia and is due respectively to terminal glomerulonephritis and malignant hypertension, is difficult. Because it is left for the pathologist to make the differentiation, the concept has grown that it is not clinically possible to establish it by study of renal function. That this is not the case we have shown by studies based on the excretions of diodrast and inulin, or urea and urinary protein, on the concentrating power of the kidneys, the urinary sediment, arterial pressure, hematocrit index and serum protein content. The studies were done in 10 patients from each group, selected because they presented the lowest levels of renal function observed in each series in the absence of the clinical syndrome of uremia.

Terminal glomerulonephritis is distinguished by a low rate of glomerular filtration, of tubular secretory capacity, and, usually, a higher rate of proteinuria than appear in malignant hypertension with renal failure. In spite of the lower level of renal excretory function in terminal glomerulonephritis, such patients survive more than four times as long as do patients with malignant hypertension in renal failure. The changes of renal function usually demonstrable in the terminal nephritic are in accord with the structural changes in the kidneys of such patients, in that they indicate lesions glomerular and capillary in locus, associated with great parenchymal destruction and fibrous replacement and suggest the frequent occurrence of large inequalities of function in the remaining nephrons.

In malignant hypertensives with renal failure, intraglomerular hydrostatic pressure seems often to be increased above the normal and the flow of blood through the residue of intact tubular tissue is diminished, the latter presumably as the result of arteriolar constriction and (afferent) arteriolar sclerosis. A subsequent communication in this series will establish the cooperation of severe arteriolar and arterial disease with renal failure as the cause of death in patients of this group. In some of these patients, in spite of greatly increased arterial pressure and presumptive constriction of glomerular efferent arterioles, intraglomerular hydrostatic pressure seems not to be increased above the normal or is even low. This observation testifies to the severity of afferent arteriolar sclerosis or constriction in these patients. The conclusion is drawn that in these, as in the terminal glomerulonephritics, the implications of functional study agree with what is known of the structural changes caused by the disease.

Evidence is obtained which suggests that the hypoproteinemia of Bright's disease, whether it occurs during chronic glomerulonephritis or in malignant hypertension with renal failure, apparently serves as a means of maintaining glomerular filtration when, in the absence of hypoproteinemia, the proportion of water filtered through the glomeruli would be grossly deficient or nil.

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DIFFERENTIAL DIAGNOSIS OF TERMINAL GLOMERULONEPHRITIS AND MALIGNANT HYPERTENSION. II. CARDIAC ASPECTS *

By R. D. Taylor, M.D., K. G. Kohlstaedt, M.D., A. B. Richter, M.D., F.A.C.P., and Irvine H. Page, M.D., F.A.C.P.,
Indianapolis, Indiana

This communication is concerned with the results of study of the heart and to a lesser extent the circulation in the same two groups of patients considered in the companion paper (Corcoran and Page [1]) with the aim of achieving the differential diagnosis. It is worth reëmphasizing that the clinical pictures resulting from terminal Bright's disease and terminal malignant hypertension with renal failure are very similar. From these similarities and their differences in courses arises the need for objective and accurate methods of differential diagnosis.

There have been numerous studies [2, 3, 4, 5, 6, 7, 8, 9] of the heart in malignant hypertension, and fewer [9, 10] in terminal glomerulonephritis. However, detailed comparison of the heart in the two morbid conditions appears not to have been made though some of its aspects have been reviewed (Page [10]). From the point of view of differential diagnosis, this is really the nub of the matter and is the object of this paper.

Methods

Ten patients with malignant hypertension and 10 with chronic glomerulonephritis were chosen from the records of the Lilly Clinic. These cases are the same as those in communication I and are identified by the first two letters of each patient's name. They were selected because of clinical similarity and represent the stage of both diseases when uremia was imminent.

Pertinent findings in each history and physical examination were selected. Venous pressure was measured in centimeters of blood rising into a tube containing citrate, connected to a No. 19 needle in an antecubital vein. Circulation time from arm to lung and arm to tongue was determined by injecting magnesium sulfate and ether intravenously. Vital capacity was determined in per cent of normal by means of the McKesson-Scott vital capacity apparatus (McKesson Appliance Co., Toledo, Ohio).

Deviation of the heart from predicted normal size was computed from two meter chest films according to the method of Ungerleider and Clark.[11] Electrocardiograms always included the conventional limb leads and one precordial lead, CFIV, and in some cases six chest leads, V_1 to V_6. Ballistocardiographic tracings were taken as described elsewhere.[12] Stroke volume,

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and cardiac output were computed from these using the area method of Starr, Rawson, Schroeder and Joseph.[13] Peripheral resistance was calculated from Bazzett, Cotton, and Laplace's formula, P.R. = 3PM/CI, (Normal 80 to 120)[14] where P.R. = peripheral resistance, P.M. = mean arterial pressure (arbitrarily, diastolic pressure + one-half of pulse pressure) and C.I. = cardiac output in liters per minute per square meter of body surface.

Results

1. History and Physical Findings. The average duration of disease in malignant hypertensives from the first symptom or sign to the present observation was five years, and in chronic nephritis 11 years (table 1). All patients with malignant hypertension complained of some degree of dyspnea of cardiac origin and in spite of the comparitive brevity of the disease, five of them developed congestive heart failure. Four of 10 malignant hypertensives complained of paroxysmal nocturnal dyspnea. The physical findings of pulmonary edema, hepatic enlargement, and dependent edema substantiated the cardiac origin of the symptoms in each case. Gallop rhythm was recorded in four of the five patients with heart failure.

In sharp contrast to this picture of cardiac failure (Grades I to IV)* developing within five years in the malignant hypertensives only one case (Grade I) occurred in the nephritic group during the course of 11 years. This patient developed congestive heart failure 33 years after onset of renal disease. Five of the ten nephritics complained of some degree of dyspnea, and edema was noted in seven. However, the absence of physical and laboratory findings of heart failure suggested other causes for these complaints. Such cause might well be the well known anemia, hypoproteinemia, and acidosis of chronic nephritis.

2. Venous Pressure, Vital Capacity, and Circulation Time. The studies of venous pressure, vital capacity, and circulation time in themselves did not differentiate the circulatory status of the two groups but merely confirmed the other findings. The venous pressure was higher, the vital capacity was lower and the circulation time was longer in the malignant hypertensives (table 1).

3. Teleroentgenograms. The degree of cardiac enlargement in the two groups was almost identical (table 2) (hypertensives + 22 per cent, range 0 to 50 per cent; nephritics + 23 per cent, range — 2.5 to 50 per cent). This equality assumes significance in light of the duration of each disease, since it suggests that malignant hypertension produces cardiac enlargement at more than twice the rate of chronic glomerulonephritis. However, the characters of the cardiac silhouettes in the two groups were quite different. Among the malignant hypertensives the shadows were bootshaped and indicated marked left ventricular enlargement. This group also showed tor-

* American Heart Association.

TABLE I

Summary of Clinical Histories and Findings

Case	Age	Years Since First Symptoms	Dyspnea Grade 1–4+	Paroxysmal Nocturnal Dyspnea	Edema 1–4+	Precordial Pain	Murmurs		Gallop Rhythm	Lungs		Liver Palpable	Venous Pressure cm. of blood	Vital Capacity per cent of normal	Circulation Time in Sec.		Course
							Systolic	Diastolic		Râles	Dullness				Arm to Tongue	Arm to Lung	
Malignant Hypertensives																	
RE	35	¾	++++		++		+		+	+		++	17	60	16	—	Died in uremia 6 wks.
CO	54	3	++	+	++	+			+	++		+++	12	81	20	12	Died in uremia 6 wks.
HI	53	7	+	+	+	+	++						10	85	14	7	Died in uremia 4 wks.
AR	52	8	++			+	+						9.5	100	17	—	Died in uremia 12 wks.
HO	49	½	++	+++				+	+	++		+	12	47	20	14	Died in uremia 6 wks.
LA	35	7	++++	+	+++					+++	++	++++	22	50	20	10	Died in uremia 12 wks.
CH	54	9	++										—	—	—	—	Died in uremia 4 wks.
GR	60	6	+++			++		+					11	71	18	8	Died in uremia 4 wks.
MC	42	2	++			++	+++						6.5	75	13	7	Died in uremia 8 wks.
ED	27	6	+		++		++	+	+	+++	++	+++	11.5	67	14	6.5	Died in uremia 4 wks.
Ave.	46.1	5											12.4	70.5	16	9	6.4 wks.
Nephritics																	
HI	40	17					+						13	85	19	—	Died in uremia 9 mos.
FR	37	20	+		+								9	110	10	5	Died in uremia 1 mo.
HA	21	6	+				+					+	7.5	90	16	7	Died in uremia 1 mo.
WI	26	2			++		+						4.5	122	11	6	Living 12 mos.
FI	22	3			++								4.5	110	26	6	Died in uremia 24 mos.
CO	27	5			+		+						9	111	11	5	Died in uremia 2 mos.
HO	49	12	+		++		+					++	—	—	—	—	Died in uremia 1 mo.
MI	30	8	+										8.5	95	15	10	Died in uremia 6 mos.
WE	50	33	+++		++	++	+++			+		+	9	86	11	7	Died in uremia 4 mos.
SM	21	6			++++								—	—	—	—	Living 7 mos.
Ave.	32.3	11.2 yrs.											7.8	100	15	6.6	6.3 mos.

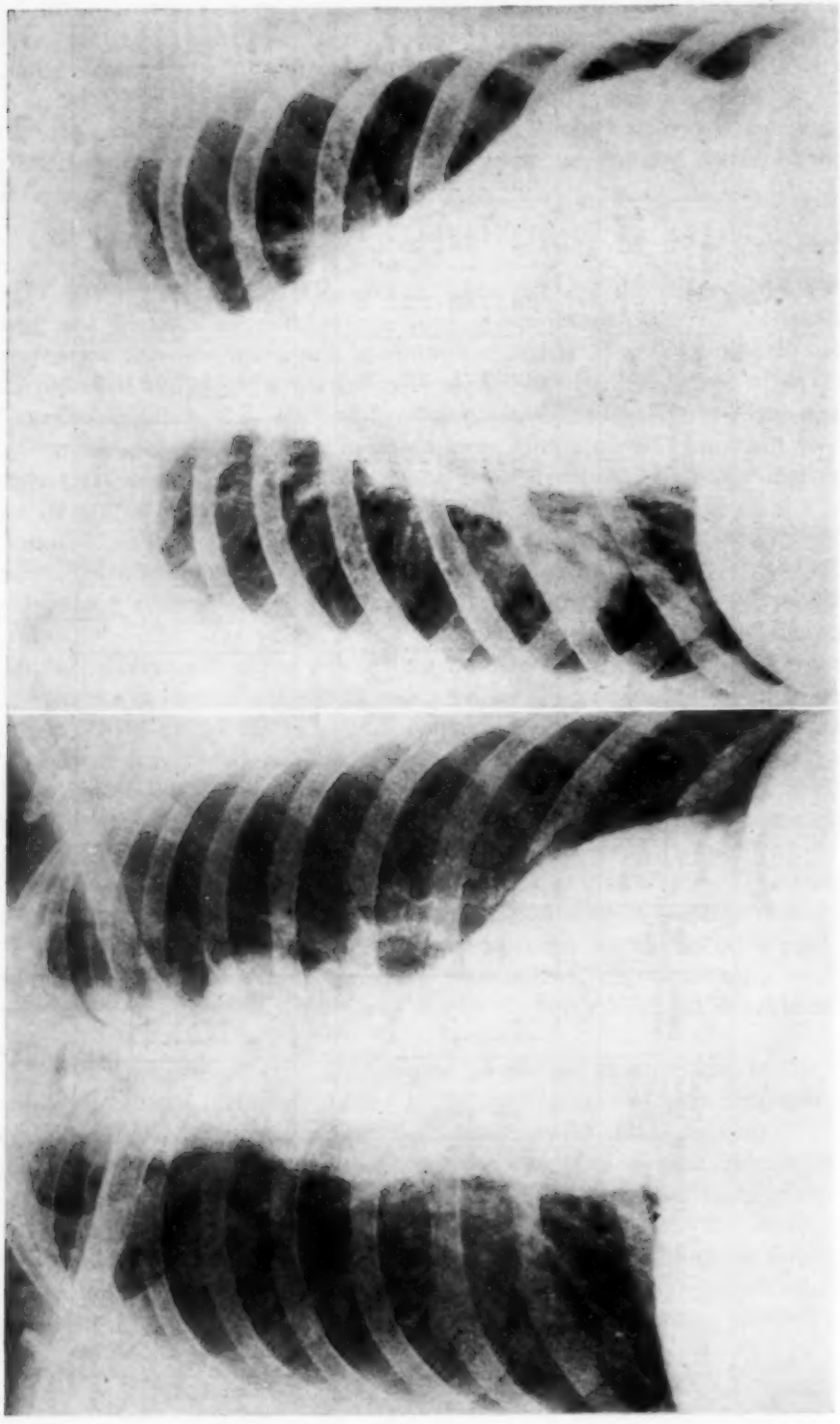

FIG. 1 (B)

FIG. 1 (A)

TABLE II

Summary of Electrocardiographic and Teleroentgenological Findings

Methods of estimation of cardiac size is explained in the text. R and S refer to these waves in the respective leads of the electrocardiogram. PC includes all precordial leads of the electrocardiogram.

Case	Pulse Rate	Receiving Digitalis	Per Cent of Cardiac Enlargement	Potential in Millivolts					Depressed ST Segment Lead				T Waves Inverted Lead				Interpretation
				R_1	R_3	S_2	S_3	R_3+S_3	1	2	3	PC	1	2	3	PC	
Malignant Hypertensives																	
RE	75	Yes	20	11	14			11									Normal
CO	100	Yes	10	7	14			7					*	*	*		Abnormal
HI	85	No	10	8	17			8	*	*		*					Abnormal
AR	90	No	20	6	18			6	*							*	Abnormal
HO	90	Yes	33	6	10		4	10	*	*		*	*				Abnormal
LA	120	Yes	50	7	8	25	7	14					*	*			Abnormal
CH	90	No	35	11	14		4	15	*	*	*	*					Abnormal
GR	85	Yes	23	11	13		5	16					*	*		*	Abnormal
Mc	105	No	29	18	18			18	*	*			*	*			Abnormal
ED	100	Yes	0	22	15	8	16	38					*	*		*	Abnormal
Nephritics																	
HI	85	No	20	10	15			10									Normal
FR	65	No	43	3	7			3									Normal
HA	88	No	32	4	8			4									Normal
WI	80	No	−2.5	7	7			7									Normal
FI	76	No	28	8	10			8									Normal
CO	70	No	22	15	14			15					*	*			Abnormal
HU	65	No	50	8	4	3	6	14									Abnormal
MI	115	No	10	13	13		10	23									Abnormal
WE	80	Yes	10	10	8		4	14					*	*			Abnormal
SM	90	No	25	9	7		5	4									Abnormal

tuosity and elongation of the aorta. One nephritic showed the same picture. The remaining nine nephritics showed generalized enlargement with globular shadows suggesting dilatation with no striking changes in the aortas (figure 1).

4. Electrocardiographic Studies. The electrocardiogram was found to aid in differentiating the two groups by pointing to greater myocardial damage among the malignant hypertensives (table 2). In this group only one patient showed an electrocardiographic pattern that was normal, whereas five such tracings were found among the nephritics. The abnormalities in both groups consisted of left axis deviation, inversion of T waves and depression of the ST segments. These last two changes were predominantly present

A. MC. Malignant hypertension. This cardiac shadow deviates 29 per cent from the predicted normal. It represents the typical left ventricular enlargement and aortic elongation and tortuosity of malignant hypertension.

B. FR. Chronic glomerulonephritis. This silhouette deviates 43 per cent from the predicted normal. It represents generalized cardiac enlargement suggesting dilatation seen in chronic nephritis. The aorta is not appreciably enlarged.

in the standard Leads I and II and occurred in nine malignant hypertensives and two nephritics. Only two tracings showed changes in Lead III and six showed ST segment or T wave changes in Leads V_5 and V_6. Pericarditis was not present in either group while these observations were being made.

5. Ballistocardiographic Studies. The clinical use of the ballistocardiograph since Henderson's original experiments [15] has been developed by Starr

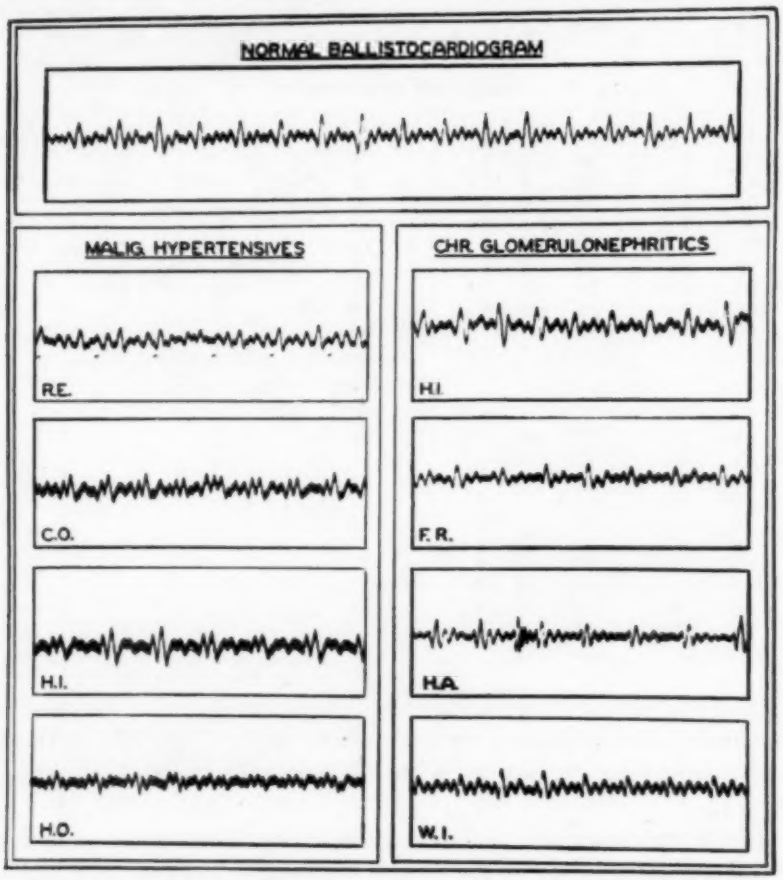

FIG. 2. Ballistocardiograms of malignant hypertensives and chronic glomerulonephritics. The tracings of the hypertensives are bizarre whereas those of the nephritics with the same degree of cardiac enlargement and almost the same arterial pressure (172 mm. Hg and 152 mm. Hg average mean arterial pressure) are almost normal.

and Schroeder.[16] The apparatus consists of a suspended bed with free longitudinal motion. The force of the blood ejected by the heart against the aortic arch and the pulmonary artery sets up ballistic impulses in the body which are transmitted to the bed and so recorded on a moving film. When the heart, great vessels and circulation are normal, a characteristic and consistently reproducible series of waves are recorded during each cardiac cycle (figure 2).

The amplitude of the first negative and positive waves express the volume of blood ejected with each heart beat. For this relationship, Starr [13] has computed formulae which permit the estimation of cardiac output in cubic centimeters per beat. Since pulse rate is also recorded, minute volume output of the heart can be calculated. Cournand, Ranges and Riley [17] compared the accuracy of these results with those attained by the direct Fick method. They were consistently lower, indicating the necessity of increas-

TABLE III

Stroke Volume, Cardiac Index, Peripheral Resistance and Ballistocardiograms

Stroke volume, cardiac index and peripheral resistance were calculated from the ballistocardiogram and mean arterial pressure. The methods are explained in the text.

Patient	Mean Arterial Pressure, mm. Hg. Diastolic and ½ Pulse Pressure	Stroke Volume c.c.	Cardiac Index L./Min./1.73 Sq. M.	Peripheral Resistance $P.R. = \frac{3MP}{C.I.}$	Ballistic Tracing
Malignant Hypertensives					
RE	203	57	2.49	244	Bizarre
CO	173	50	2.58	201	Bizarre
HI	194	33	1.91	304	Bizarre
AR	149	41	2.13	210	Bizarre
HO	169	53	3.00	169	Bizarre
LA	165	61	2.64	188	Bizarre
GR	165	45	1.80	275	Bizarre
ED	159	44	2.13	224	Bizarre
Ave.	172	48	2.34	227	
Nephritics					
HI	149	65	3.67	122	Normal
FR	124	58	2.41	154	Slightly abnormal
HA	155	47	2.49	187	Normal
WI	145	51	2.39	182	Normal
CO	150	51	1.90	237	Normal
HU	141	77	2.93	144	Normal
MI	201	37	1.86	324	Slightly abnormal
WE	155	46	2.49	187	Bizarre
Ave.	152	54	2.52	192	

ing the final value for stroke volume by 18.5 per cent. This correction was made in our data.

Eight patients in each group were studied in this way.

a. Characteristics of Ballistocardiographic Tracings. All of the malignant hypertensives had ballistic tracings that were bizarre (table 3). By this we mean the waves were so distorted in their relationship one to the other and to the base line as to be completely unlike the normal pattern (figure 2). On the other hand, the nephritics' ballistocardiograms were in

most (five of eight) cases normal, and the abnormalities that were present were not sufficient to obscure the normal pattern except in the one who had developed congestive heart failure. Simple inspection of the ballistic patterns thus aided in the differentiation of the two diseases in 15 of the 16 cases studied.

b. Blood Pressure, Stroke Volume, Cardiac Output, and Peripheral Resistance. These hemodynamic studies had little significance either as individual tests or in individual cases, but taken collectively they showed a definite trend (table 3).

The average mean arterial blood pressure of the malignant hypertensives was higher than that of the nephritics (172 mm. Hg as compared to 152 mm. Hg), and the average stroke volume and cardiac output were smaller (48 c.c. and 2.34 L./min./sq. M. of body surface as compared to 54 c.c. and 2.52 L.). Since peripheral resistance is calculated from these values, that of malignant hypertension must be greater than that of chronic nephritis (227 as compared to 192). This difference of 18 per cent is not great in light of the normal variation of 80 to 120. This wide range of normal is due to the variation of normal arterial pressure while normal cardiac output is usually a constant function. In contrast, arterial pressure was greatly and consistently elevated in all our patients, and cardiac output was depressed in many. The variability of peripheral resistance found in normal people may not apply to such abnormal circumstances. We incline, therefore, to the view that peripheral resistance or sclerosis or both is greater in malignant hypertension than in chronic nephritis.

Discussion

The preceding paper presented groups of 10 clinically similar cases of malignant hypertension and of chronic glomerulonephritis, and showed how differentiation may be made by studies of renal function. In this report we have analysed the cardiac and circulatory functions of these same patients with the hope of further aiding the differentiation.

It was pointed out in the first paper that nephritic patients can survive, and with suitable care in comparative comfort, with much less functioning renal tissue than can patients with malignant hypertension. It was concluded that factors other than renal failure were probably responsible for disability and death in the malignant hypertensives. The data presented here substantiate this by demonstrating a more severe and rapidly progressive disease of the heart and blood vessels in malignant hypertension. Cardiac and renal failure, therefore, are joint factors in the mortality of malignant hypertension.

The cardiac enlargement demonstrated by roentgenogram as being present in equal degrees in the two groups could have resulted from either hypertrophy or dilatation. The extent to which each of these mechanisms participated is not certainly known. However, as we have seen, the uniform

enlargement of heart and aorta in the nephritics suggests in them a preponderance of dilatation over hypertrophy (Fishberg [18]). The reverse is true in the malignant hypertensives whose enlargement was largely that of the left ventricle and whose aortas were both elongated and tortuous. Thus it seems likely that the equality of cardiac enlargement in the two groups was achieved by somewhat different mechanisms.

The greater degree of hypertrophy in the malignant hypertensives may be explained on two bases: (*a*) As an adaptation to a greater peripheral resistance, and (*b*) on less certain grounds, as an expression of greater coronary arterial and arteriolar sclerosis or constriction or both. This first suggestion is based on the observation of greater peripheral resistance and vascular disease in malignant hypertensives, the latter on the demonstration by Dauber and Katz [19] of ventricular hypertrophy in cholesterol atherosclerosis of chicks. Since the heart's weight is an index of its hypertrophy, the justness of the view that hypertrophy is more common in malignant hypertension is borne out by the finding that the hearts of such patients weigh more than do those of chronic nephritics (MacMahon and Pratt [8]). The uniform character of cardiac enlargement in chronic nephritis, presumably the result of overall dilatation, is not easily explained.

The tortuous and elongated aortas seen in malignant hypertension could be due, in part, to the different ages of the two groups (average 32 years in nephritis and 46 years in malignant hypertension), since the aorta loses elasticity and increases in size with passing years. Thus, according to Ungerleider and Gruber [20] 14 years aging in these decades would result in an aortic diameter 0.47 cm. greater at age 46 than at age 32. An estimation of the internal diameter of the aorta at 32 and 46 years of age (Bazzett [14]) shows a difference of 0.83 cm. But this can not be the whole story, since three malignant hypertensives of 35 years and under showed the same aortic pattern as did the older hypertensives whereas three nephritics of 37, 49 and 50 years of age did not. It would seem more probable that the greater stress and strain and small vessel sclerosis of malignant hypertension result in more aortic injury than develops in nephritis.

The electrocardiographic changes usually associated with hypertensive heart disease are left axis deviation, depressed ST segments, and inverted T waves in the standard and precordial leads. These patterns have been variously called chronic left ventricular strain (Barnes and Whitten [21]), coronary insufficiency and hypertrophy (Master [22]), impaired conduction pathways (Katz [23]), left ventricular hypertrophy (Gruber and Ungerleider [24]) and coronary artery sclerosis (Levine [25]). Experimentally the Robbs [26] have produced left axis deviation by dissecting away the exposed left ventricle of the dog and T wave changes by stretching the muscle fibers of the dog's left ventricle.[27] Hoff, Nahum and Kisch [28] have produced similar changes in the dog by applying cold and potassium chloride to the exposed ventricle. Certainly one or a combination of two or more of these clinical and ex-

perimental mechanisms must play a part in the production of the electrocardiogram characteristic of hypertensive heart disease.

In our cases the incidence of left axis deviation, T wave and ST segment changes was 3 to 1 in favor of malignant hypertension. In 10 malignant hypertensives there was only one normal tracing, whereas five were found among the nephritics. This frequency of normal electrocardiograms in chronic nephritis was formerly noted by Richter and O'Hare.[10] Consideration of the electrocardiographic findings can leave little doubt that the myocardial damage of malignant hypertension is more severe than that of chronic glomerulonephritis. Therefore, given a patient with findings common to both diseases and a normal electrocardiogram, the weight of evidence is in favor of chronic glomerulonephritis.

The most definitive differentiation of the cardiac status in these two conditions was furnished by simple inspection of the ballistocardiograms. Starr and Schroeder [18] were struck by the frequency of normal ballistic forms in the presence of gross cardiac abnormalities, emphasizing the adaptability of the heart muscle to disease. In the nephritic group, this compensatory mechanism made for almost normal tracings in all but one patient whereas those of the hypertensives were all bizarre. These data indicate that the heart of the malignant hypertensive is unable to compensate for its disabilities as well as the nephritic's heart.

The mechanism of the production of these consistently bizarre patterns of malignant hypertension is not known. The pronounced aortic abnormalities seen in the teleroentgenograms may be important. As we have suggested, these aortas are less elastic than those of the chronic nephritics who had less elongation and tortuosity. Since the target of blood ejected from the left heart is the arch of the aorta, distortion of this surface and loss of its elasticity could contribute to the more abnormal ballistocardiograms of malignant hypertension. In addition, the swings of the ballistocardiograph are dependent upon the impact of blood against both the arch of the aorta and the curve of the pulmonary artery. The rapidly enlarging and abnormal left ventricle of malignant hypertension may throw its stream of blood with greater comparative force than the more normal right ventricle whose pulmonary vascular resistance, at least in hypertensive dogs (Katz [29]), is not increased. It may also inject it into the aorta at a different and abnormal angle. The combination of these two mechanisms, cardiac and aortic, would offer an adequate explanation for the great discrepancy in the ballistocardiograms produced by equally enlarged hearts against almost the same arterial pressure.

Taylor and Page [12] suggested that the cardiac output was related to mean arterial pressure and cardiac size, i.e., cardiac output was proportional to: $\frac{\text{Cardiac size in per cent of normal}}{\text{Mean arterial pressure}}$. The malignant hypertensives with slightly higher arterial pressure and roughly the same sized hearts should

thus have smaller cardiac outputs. This was observed here. It is a reflection of greater peripheral resistance in malignant hypertension which probably means more severe and more generalized arteriolar constriction or sclerosis or both.

The preceding paper presented evidence that factors other than renal failure were probably responsible for the fulminant course and early death of malignant hypertensives as compared to chronic nephritics. More severe heart disease and more generalized blood vessel disease in malignant hypertension seemed to be plausible explanation for this difference. The present study substantiates that view and therefore offers a useful diagnostic aid and means of offering prognosis in those stages of malignant hypertension and chronic glomerulonephritis which are superficially so alike. The significance of this assumes more than academic importance in view of the distinct survival periods of each group. The average survival period was one month among the malignant hypertensives and eight months or more among the chronic nephritics.

The diagnosis, when it is in question, may usually be made by evaluation of the cardiac change in terms of clinical signs and symptoms, of roentgenographic shadows, of electrocardiographic abnormalities, by the degree of increased peripheral resistance, and especially by the character of the ballistocardiographic pattern.

Summary

1. The cardiac status of 10 patients with malignant hypertension in whom uremia was imminent was compared to that of 10 clinically similar chronic glomerulonephritics.

2. Five of 10 malignant hypertensive patients developed clinical signs of heart failure in an average disease duration of five years, whereas only one nephritic developed congestive failure in a group average of 11 years.

3. In these two periods the same degree of cardiac enlargement developed in both groups. In malignant hypertension the enlargement was primarily left ventricular and the aortas were long and tortuous. In nephritis the enlargement was globular and suggested dilatation.

4. Electrocardiographic evidence of hypertensive heart disease is usual in malignant hypertension and rare in chronic nephritis.

5. All of the malignant hypertensives had bizarre ballistocardiograms. This abnormality occurred in only one nephritic in whom it was associated with heart failure.

6. The blood pressure of malignant hypertension is usually higher, cardiac output is lower and peripheral resistance is greater, indicating more severe peripheral vasoconstriction or sclerosis or both as compared to chronic glomerulonephritis.

7. The differential diagnosis between terminal malignant hypertension and terminal glomerulonephritis can be made by detailed study of the heart

and circulation. Evidences of advanced heart disease are usual in malignant hypertension, whereas they are often indistinct or absent in nephritis.

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RUPTURE OF THE HEART IN MYOCARDIAL INFARCTION. EXPERIENCE IN A LARGE GENERAL HOSPITAL*

By SIDNEY FRIEDMAN, M.D., and PAUL D. WHITE, M.D., F.A.C.P.,
Boston, Massachusetts

SPONTANEOUS rupture of the heart, although always a dramatic episode and recognized as a pathological curiosity since the Middle Ages, has a clinical significance that is not even yet adequately recognized. For this reason and especially because of the finding of a high incidence of cardiac rupture among psychotic patients with acute myocardial infarction reported in a companion paper in this journal,[1] it was thought wise to determine the frequency and circumstances of rupture of the heart in a large general hospital in the same part of the country and among persons of age and social status comparable to those of the psychotic cases.

Martland,[2] in 1940, in his rôle of medical examiner, reported finding rupture of the myocardium as a cause of death in 42 (2.1 per cent) of 2,000 cases of individuals who died suddenly; all of the 2,000 cases were over 10 years old, the majority between 40 and 65, five-sixths males and one-sixth females. In this same series coronary occlusion with thrombosis was present in 304 cases, coronary occlusion without thrombosis in 314 cases, "coronary insufficiency" in 112 cases, and aneurysm of the left ventricle in 59 cases.

Among 25,000 postmortem examinations at the Los Angeles County Hospital from 1924 to 1941 there were 865 cases of unhealed myocardial infarction, of which 72 (8 per cent) showed cardiac rupture.[3]

Present Study. Among 2,967 autopsies performed at the Massachusetts General Hospital, between March 1933 and November 1940, the protocols of 270 cases with myocardial infarction were found and analyzed. Of this number 105 had suffered recent myocardial infarction and the remaining 165 showed old coronary occlusion with healed infarction. In this latter group numerous ventricular aneurysms were found but not a single case of rupture occurred. Of the 105 cases of acute infarction, all occurring within two weeks of death, 10 had as the immediate cause of death a rupture of the ventricle with tamponade from hemopericardium.

CASE REPORTS

Case 1. Protocol No. 6697 is that of an 80 year old male who was well until seven days before his death when he developed slight pain in his left axilla without fever or dyspnea. His blood pressure, which had been 160 mm. mercury systolic and 80 mm. diastolic, was found to be 110 mm. systolic and 70 mm. diastolic. The day fol-

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From the Cardiac Laboratory of the Massachusetts General Hospital, Boston, Massachusetts.

TABLE I

Summarizing the Data of Our Ten Cases of Cardiac Rupture

Age	Sex	Duration from Clinical Onset	Sedation	Previous Cardiac History	Pathological Findings
79	M	9 days	Adequate	Angina pectoris for 3 months. Hypertension of variable period	Heart enlarged. Occl. of d.b. of L.C.A.
66	M	2 days	Inadequate	None	Heart slightly enlarged. Occl. of d.b. of L.C.A. L.V. infarct and laceration
80	M	7 days	Adequate but not kept in bed because of uncertainty of diagnosis	Slight hypertension	Heart moderately enlarged. L.V. infarct and perforation. Occl. of d.b. of L.C.A.
64	F	12 hours	Inadequate because of violence, result of cerebral thrombosis	Angina pectoris for 5 years. Hypertension	Heart not enlarged. Occl. d.b. of L.C.A. Infarct of L. and R. ventricle
67	F	4 days	Inadequate because of violence due to cerebral thrombosis	Hypertension	Heart moderately enlarged. Occl. of circumflex branch of R.C.A. Infarction of posterior surface of L.V. with perforation
62	M	14 days	Adequate	Angina pectoris for 1 month	Occl. of d.b. of L.C.A. and circumflex branch of the right. Heart moderately enlarged. Infarction of L.V. with perforation
51	M	14 hours	Adequate		Heart slightly enlarged. Occl. of d.b. of L.C.A. Infarct and perforation of L.V.
55	M	12 hours	Adequate	Angina pectoris for 2½ wks.	Heart not enlarged. Occl. of d.b. of L.C.A. Infarct of L.V. with perforation
66	F	2 days	Inadequate	No history	D.B. of L.C.A. occl. Heart not enlarged. Infarct of left ventricle with laceration
67	M	4 days	Adequate	Angina pectoris for 2 months	Circumflex branch of L.C.A. occl. Infarct of left ventricle with laceration

L.V.—left ventricle.
R.V.—right ventricle.
L.C.A.—left coronary artery.
R.C.A.—right coronary artery.
occl.—occlusion.
d.b.—descending branch.

lowing this episode râles were found in his lung bases and an irregular pulse was noted. Five days later he was found to have slightly more congestion, and an electrocardiogram showed T waves consistent with acute coronary occlusion. He was found

dead in bed the following day. Postmortem examination revealed 350 c.c. of blood in the pericardial sac. The heart weight was 450 grams. An area of acute infarction of the left ventricle, 5 cm. in diameter, was found with a small perforation in the center. The descending branch of the left coronary artery was occluded by a fresh thrombus.

Comment: This man died quite suddenly when he appeared to be "getting better." He had been seen within a few minutes of his death and did not then appear very ill.

Case 2. Protocol No. 7116 is that of a 67 year old female, known to have diabetes and hypertension, who, four days after a cataract operation, developed diabetic acidosis which was treated vigorously. The next day she complained of pain in the left chest. A slight elevation of temperature and râles in both lung bases were found. Her temperature continued to rise and she became restless and disoriented and thrashed about to get out of bed; four days after the first onset of chest pain she developed hemiplegia, collapsed, and died. Postmortem examination revealed 900 c.c. of blood in the pericardial sac; heart weight 450 grams. There was a recent infarct of the posterior surface of the left ventricle with perforation through a soft saccular aneurysm. The circumflex branch of the right coronary artery was found to be occluded by a recent thrombus.

Comment: In this case violence may have contributed to the myocardial rupture.

Case 3. Protocol No. 7204 is that of a 64 year old female admitted to the hospital for symptoms of intestinal obstruction of two weeks' duration. She was known to have hypertension and diabetes, and she had suffered from angina pectoris for five years. While being examined she suddenly developed severe precordial hyperesthesia and apparent pain, thrashed about, collapsed, and died 12 hours after admission to the hospital. Postmortem examination revealed 250 c.c. of blood in the pericardial sac; the heart weight was 725 grams. There was a recent infarct of the left and right ventricles. All coronary vessels were markedly arteriosclerotic. There was a fresh thrombus in the descending branch of the left coronary artery. Recent infarcts were observed in the lenticular nuclei of the brain.

Comment: Violence, because of the patient's mental state, may have contributed to the final episode of myocardial rupture.

Case 4. Protocol No. 7485 is that of a 66 year old female who had a typical attack of coronary thrombosis two days prior to her death. Death was sudden and no further information was available. Postmortem examination revealed 200 c.c. of blood in the pericardial sac and a heart weight of 250 grams. Two lacerations were seen on the anterior aspect of the left ventricle in the center of the recently infarcted myocardium. The descending branch of the left coronary artery was occluded by a fresh thrombus.

Comment: No apparent physical strain was to be blamed for the rupture in this case.

Case 5. Protocol No. 7513 is that of a 66 year old male who was admitted to the hospital because of the sudden onset of retrosternal pain with vomiting and perspiration of two days' duration. On examination he exhibited gallop rhythm but no friction rub. The white blood count was 13,500. He died quite suddenly while being examined, 72 hours after the onset of his pain. On postmortem examination the pericardial sac contained 200 c.c. of blood; heart weight 350 grams; two-thirds of the left ventricle showed recent infarction, in the center of which was a laceration about 3.5 cm. in length. The descending branch of the left coronary artery was completely occluded by old and new thrombi.

Comment: Except for whatever exertion was involved in the process of examination, no apparent cause other than the infarct itself was found for this final episode.

Case 6. Protocol No. 7591 is that of a 79 year old male who suffered from

angina pectoris three months before his admission to the hospital. Six days before admission he was seized, after a walk, with severe precordial pain, only slightly relieved by sedatives. The pain persisted for six days with varying severity. When examined at the hospital, his blood pressure was found to be 150 mm. mercury systolic and 100 mm. diastolic, temperature 99.8° F., pulse rate 110, white blood count 24,000. His electrocardiogram showed changes typical of anterior myocardial infarction. On the third day after his admission, while in bed, he suddenly became cyanotic and died within a few seconds. Postmortem examination revealed 500 c.c. of blood in his pericardial sac; the heart weight was 375 grams and there was an area of infarction about 7 cm. in diameter, in the center of which was a small laceration. The descending branch of the left coronary artery showed a blackish red adherent thrombus.

Comment: No evidence could be obtained to show any cause other than the infarct itself or any premonitory symptoms for this final episode of cardiac rupture.

Case 7. Protocol No. 7779 is that of a 62 year old male who suffered from mild angina pectoris for one month previous to a sudden seizure of substernal pain coming after lunch. On examination no friction rub was heard. The blood pressure was 130 mm. mercury systolic and 100 mm. diastolic; pulse rate 72, temperature 102° F. Morphine relieved the pain. Two days later while in bed he was awakened by a severe substernal pain. His pulse rate was 120, white blood count 26,800, temperature 100° F. Gallop rhythm was found. The blood pressure fell to 180 mm. Hg systolic and 75 mm. diastolic. A friction rub was heard after the fifth day of his attack. Temperature and pain continued for a total of 10 days and there were no more subjective symptoms. The patient was resting comfortably in bed and apparently doing well when he was found dead on the fourteenth day after the onset of his illness. Postmortem examination revealed 500 c.c. of blood in the pericardial sac; heart weight 400 grams. There was a recent infarct of the left ventricle, in the center of which was a small laceration. The descending branch of the left coronary artery showed a deep-red soft thrombus and the right circumflex showed a reddish-gray thrombus.

Comment: No cause in the way of special strain could be blamed for this final myocardial rupture.

Case 8. Protocol No. 8387 is that of a 67 year old male physician who, for two months before admission, suffered from angina pectoris which had increased in frequency and severity. Two days before admission he suffered severe, continuous substernal pain of two and a half hours' duration. His white blood count was 11,500, pulse rate 84. An electrocardiogram showed signs suspicious of myocardial infarction. He was given fairly heavy sedation for 48 hours, then suddenly became cyanotic and died. Postmortem examination revealed 500 c.c. of blood in the pericardial sac. There was a 1.5 cm. laceration of the left ventricle. The circumflex branch of the left coronary artery was occluded by a grayish-pink granular friable clot.

Comment: Despite heavy sedation in this case cardiac rupture took place.

Case 9. Protocol No. 9393 is that of a 51 year old male who was admitted to the hospital with severe crushing substernal pain of two hours' duration. There was no past history of angina pectoris or hypertension. Temperature was 99.6° F., pulse rate 90, blood pressure 130 mm. mercury systolic and 80 mm. diastolic, white count 13,000. No friction rub was heard. An electrocardiogram showed a typical anterior infarction. The pain persisted and twelve hours after admission he suddenly went into collapse and died. Postmortem examination revealed 500 c.c. of blood in the pericardial sac; heart weight 375 grams. There was a 5 cm. area of recent infarction of the left ventricle in the center of which was a 3 cm. laceration. The descending branch of the left coronary artery showed a fresh red-brown thrombus.

Comment: Death from cardiac rupture came quickly and unexpectedly in this patient.

Case 10. Protocol No. 9779 is that of a 55 year old male who was seized with attacks of substernal pain radiating down both arms and into the wrists, lasting about one minute, not definitely related to effort, and not affected by nitroglycerine. There were five to 10 attacks each day. An electrocardiogram taken six days after onset was negative. Two and a half weeks after the onset of these seizures he was awakened from sleep with an agonizing substernal pain which lasted five hours. He was given ½ grain of morphine with relief. Three hours later he developed cyanosis and congestion and 12 hours after the onset of this attack he died. Postmortem examination revealed 1,200 c.c. of blood in the pericardial sac. There was a jagged laceration 3 cm. in length in the left ventricle. There was a soft, thin, flabby area of recent myocardial infarction about 7 cm. in diameter. The descending branch of the left coronary artery showed a gray-red, firmly adherent thrombus 1.3 cm. in length.

Comment: In spite of the negative electrocardiogram this process had probably been going on for a period of two weeks and the terminal episode indicated an extension of the process with myocardial rupture. He had not been confined to bed until the last 12 hours of his life.

Summary and Conclusions

Cardiac rupture occurred in 10 cases, or 3.7 per cent, of a series of 270 instances of myocardial infarction found among nearly 3,000 autopsies at the Massachusetts General Hospital from 1933 through 1940. All 10 cases of cardiac rupture were found among the 105 patients with acute myocardial infarction (9.5 per cent) and none among the 165 cases of old infarction.

The average age of our 10 cases was 65.7 years and the sex incidence was seven males and three females.

Death always ensued quite rapidly after the occurrence of the rupture, as evidenced by the state of the blood in the pericardial sac and the condition of the lacerated tissue.

All 10 deaths occurred in less than two weeks after the clinical onset of acute myocardial infarction, most of them within a period of two to 10 days after the illness began.

In eight of the 10 cases the descending branch of the left coronary artery and the anterior wall of the left ventricle were involved. In one case the circumflex branch of the left coronary was thrombosed and in the remaining case the circumflex branch of the right coronary.

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RUPTURE OF THE HEART IN PATIENTS IN MENTAL INSTITUTIONS*

By WALTER W. JETTER, M.D., and PAUL D. WHITE, M.D., F.A.C.P.,
Boston, Massachusetts

THE desirability of recognizing the presence of a myocardial infarct in its earliest stage and of instituting promptly a régime of sedation and bed rest has long been one of the cardinal precepts of clinical practice. It is generally believed that by reducing the physiological demands upon the damaged myocardium to a minimum the danger of rupture is decreased and the likelihood of repair is enhanced.

The postmortem findings in a series of ambulant mentally ill persons in whom sudden collapse and death were unexpected because of absence or perversion of subjective reaction to visceral disease have provided striking confirmation of the importance of early diagnosis and bed rest in the treatment of myocardial infarction. In the series of cases to be reported herewith it was found that 16, or 73 per cent, of a total of 22 patients with acute myocardial infarction died of cardiac tamponade due to rupture at the site of a recent infarct.

Selection of Material. Attached to the central administrative organization of the Massachusetts Department of Mental Health is a pathological service for investigating sudden, obscure, and traumatic deaths occurring in mental hospitals. A recent series of 115 consecutive autopsies conducted under the jurisdiction of that service included 69 deaths due to heart disease. Of these obliterative coronary arteriosclerosis was the etiological factor in 61 instances. No visible infarction was evident in 14, whereas in the remaining 47 the following incidence of myocardial infarction was observed: old infarcts only, 25 cases; recent infarcts only, 12 cases; old and recent infarcts combined, 10 cases. Of the 22 hearts containing recent infarcts 16 had ruptured.

Summary of Cases. Table 1 summarizes the clinical findings in the 16 cases of cardiac rupture. Ten were male and six were female. The mean age was 66.5 years and in only one instance was the decedent younger than 50.

Routine physical examinations made at periodic intervals in the 16 patients, most of whom had been institutionalized for years, showed a moderate to severe chronic hypertension in 14 instances. In only one case was there a history of previous angina pectoris and in this instance autopsy revealed a healed myocardial infarct (case 2). In 10 instances patients were

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From the Department of Legal Medicine, Harvard Medical School, and Massachusetts Department of Mental Health, and the Cardiac Laboratories of the Massachusetts General Hospital, Boston, Massachusetts.

ambulatory and in apparent good health until they suddenly collapsed and died. In four cases there were vague complaints two to 72 hours prior to death, for which bed rest had been ordered in two instances. These two

TABLE I

Summary of Clinical Data of 16 Cases of Cardiac Rupture

Case	Sex	Age	Mental Diag.	Length Hosp. Stay (yrs.)	History of Angina Pectoris	Duration of Symptoms before Acute Collapse and Death	History of Hypertension	Bed Rest
1	M	72	Imbecile	20	No	3 days (vague)	Yes	Partial
2	M	62	Dem. precox paranoid	21	Yes	None	Yes	None
3	M	77	Alc. psych. Chronic hallucinosis	22	No	11 hrs.	Yes	Complete*
4	F	62	Paranoid condition	12	No	13 hrs.	Yes	Complete*
5	F	67	Dem. precox heb. type	35	No	None	Yes	None
6	M	64	Org. dis. CNS	12	No	2½ hrs.	Yes	None
7	M	64	Dem. precox paranoid	18	No	None	Yes	None
8	F	61	Manic depressive—depressed	16	No	None	Yes	None
9	M	83	Dem. precox paranoid	38	No	None	No	None
10	F	68	Dem. precox paranoid	22	No	None	Yes	None
11	F	63	Dem. precox catatonic	13	No	None	Yes	None
12	F	72	Undiagnosed	0.08	No	None	Yes	None
13	M	67	Epilepsy	40	No	None	Yes	None
14	M	48	Manic depressive—manic	4	No	28 hrs.	No	Partial
15	M	75	Senile psych.	4.5	No	72 hrs.	Yes	Partial
16	M	66	Paranoia	0.5	No	None	Yes	None

* Bed rest incident to subepicardial hematoma.

individuals died when they got out of bed to go to the bathroom. In the other two cases (cases 3 and 4) there was serious collapse 11 and 13 hours prior to death. This collapse was apparently incident to the development

of a subepicardial hematoma which became progressively larger until its final rupture into the pericardial cavity.

Table 2 summarizes the pathological findings in the 16 cases. Arbitrarily considering a heart to be enlarged if its weight exceeded 400 grams in the male and 350 grams in the female, seven of the 10 male and four of the six female hearts were hypertrophied. The site of the acute infarct involved the left ventricle alone in eight instances, the left ventricle and interventricular septum in seven instances, and both the left and right ventricles and the interventricular septum in the sixteenth case. The infarcts were characteristically large and averaged 4 to 5 centimeters in diameter. In appearance they were soft, friable, and usually a mottled yellow-red, with hemorrhagic foci close to the site of perforation. An early fibrinous pericarditis was present in 10 instances, and endocardial thrombi were present in nine.

The ruptures were usually in the centers of the most recent infarcts and were situated in the left ventricle in 15 instances and in the right in one. The margins of the defects were ragged, hemorrhagic, and friable. Occasionally there were multiple defects in close relation to each other. Although there was always some subepicardial hemorrhage, hematomas of significant size were observed in only three instances (cases 3, 4, and 5).

Multiple blocks of myocardium were taken for histological examination in 15 of the 16 cases. They were stained routinely with hematoxylin and eosin, and occasionally with phosphotungstic acid and Van Gieson's connective tissue and Sudan III stains. An estimation of the approximate age of the infarcts was based on an adaptation of the criteria of Mallory, White, and Salcedo-Salgar.[1] Stage 1 included lesions characterized by early coagulation necrosis of the myocardium with little or no exudation. These were regarded as being less than 24 hours old. Stage 2 comprised lesions in which the necrotic muscle was infiltrated by polymorphonuclear leukocytes. These infarcts were considered to be between one and six days old. Infarcts showing active fibroblastic repair were placed in Stage 3 and were considered to be between one and three weeks in age. In Stage 4 were assigned infarcts cicatricial in character.

In judging the age of an infarct it is essential that the proper sites for histological examination be selected. Healing begins on the periphery of the lesion, proceeding from contiguous living tissue, and then gradually extends inward. During the early weeks as the healing reparative process continues, it is usually the case that different phases are present in different parts of the infarct, that of greatest age occurring at the periphery. Significant sections, therefore, should be taken from the margin of the infarct, and for the purpose of orientation it is preferable that adjacent uninvolved myocardium be included.

Not only do different regions of the same infarct show differences in completeness of destruction and extent of repair but there is always a pos-

TABLE II

Summary of Autopsy Data of 16 Cases of Cardiac Rupture

Case	Age	Sex	Ht. Wt. (gms.)	Site Recent Infarction	Size Infarct. Dia. Cms.	Site of Defect	Epicardial Fibrin	Endocardial Thrombi	Old Infarction	State of Coronary Arteries				Microscopic Examination		Complicating Cardiac Lesions	Significant Subepicardial Hemorrhagic Extravasation	Acute Cardiac Aneurysmal Dilatation
										Fresh Thrombus	Organized Thrombus	Hemorrhage into Atherosclerotic Plaque	Obstructing Sclerosis without Occlusion	Number of Recent Infarcts Contiguous with Site of Rupture	Estimated Age of Most Recent Infarct			
1	72	M	540	LV IVS	7	LV	+	+	0	—	DRLC	DRLC	DRLC CRLC	Single	1–2 wks.	Aortic insufficiency	0	0
2	62	M	570	LV	3.5	LV	+	+	+	CRLC CRRC	DRLC	—	All	Multiple	2–6 days	None	0	0
3	77	M	460	LV IVS	4–5	LV IVS	0	+	+	DRLC	DRLC RC	—	DRLC CRLC	Single	2–6 days	Aortic stenosis	+	0
4	62	F	420	LV	2	LV	0	+	0	—	RC CRLC	—	RC LCA DRLC	Single	1–2 wks.	None	+	0
5	67	F	550	IVS LV	8	LV	0	0	0	CRLC	CRLC DRLC	—	All	Single	2–4 days	Mitral stenosis. Extensive pericardial synechiae	+ —	0
6	64	M	520	IVS LV	9	LV	+	+	0	DRLC	DRLC CRLC	—	DRLC CRLC	Multiple	2–4 days	Aortic and mitral insufficiency	0	+
7	64	M	440	IVS LV	8	LV	+	+	+	DRLC	DRLC RC	—	RC DRLC DRRC	Single	1–2 wks.	None	0	+
8	61	F	300	LV	5	LV	0	+	0	—	—	—	RC DRLC	Single	2–6 days	None	0	0

LV—left ventricle.
RV—right ventricle.
IVS—interventricular septum.
LCA—left coronary artery.
DRLC—descending ramus left coronary artery.
CRLC—circumflex ramus left coronary artery.
CRRC—circumflex ramus right coronary artery.
DRRC—descending ramus right coronary artery.

RV—right ventricle.
IVS—interventricular septum.
LCA—left coronary artery.
CRLC—circumflex ramus left coronary artery.
CRRC—circumflex ramus right coronary artery.
DRRC—descending ramus right coronary artery.

TABLE II—*Continued*

Case	Age	Sex	Ht. Wt. (gms.)	Site Recent Infarction	Size Infarct. Dia. Cms.	Site of Defect	Epicardial Fibrin	Endocardial Thrombi	Old Infarction	State of Coronary Arteries				Microscopic Examination		Complicating Cardiac Lesions	Significant Subepicardial Hemorrhagic Extravasation	Acute Cardiac Aneurysmal Dilatation
										Fresh Thrombus	Organized Thrombus	Hemorrhage into Atherosclerotic Plaque	Obstructing Sclerosis without Occlusion	Number of Recent Infarcts Contiguous with Site of Rupture	Estimated Age of Most Recent Infarct			
9	83	M	350	RV IVS LV	4	RV	0	0	0	DRLC	—	—	RC DRLC	Single	2–4 days	Mitral stenosis	0	0
10	68	F	340	IVS LV	3	LV	+	0	+	—	—	—	DRLC RC	Single	2–4 days	None	0	0
11	63	F	475	LV	4	LV	+	+	0	—	DRLC CRLC	—	RC DRLC CRLC	Multiple	2–4 days	None	0	0
12	72	F	475	LV	4	LV	+	+	+	RC DRLC CRLC	DRLC	—	All	Single	2–3 wks.	None	0	+
13	67	M	300	LV	5	LV	+	0	0	—	DRLC	—	RC DRLC	—	—	None	0	0
14	48	M	360	LV	5	LV	+	0	0	—	—	—	DRLC CRLC	Single	1–2 wks.	None	0	0
15	75	M	500	LV	6	LV	0	0	0	CRLC	—	CRLC	CRLC DRLC CR	Single	2–4 days	None	0	0
16	66	M	510	LV IVS	5	LV	+	0	0	—	—	—	CRLC DRLC	Single	2–3 wks.	None	0	0

sibility that additional infarction has occurred in a region of previous infarction. Such areas may be detected in the type of reparative process.

Assuming the presence of a single large infarct it should be appreciated that it is not always possible to secure sections which include normal muscle, periphery of infarct, and enough of the more centrally located regions to observe the gradual transition in the age of the reparative process. Particularly is this made difficult by the fact that the periphery of an infarct is usually composed of a number of finger-like projections which interdigitate with projections of normal myocardium. Hence a cross section through such an area might show alternating ovoid or circular areas of normal and infarcted muscle.

In the 15 cases in which microscopic examinations were made the site of rupture in 12 apparently represented a single episode of infarction, whereas in three the rupture occurred at the site of mixed acute and less recent infarct. Of the 12 hearts in which rupture occurred at the site of a single episode of infarction four were estimated to be between two and four days old, two were between two and six days in age, four between one and two weeks, and the remaining two cases were between two and three weeks old. Of the three cases in which infarcts of different ages were recognized at the site of rupture there were two in which the most recent infarct appeared to be from two to four days old and one from two to six days old.

Case Reports

Case 1. History. The deceased was an imbecilic white male of 72 years who had resided in state institutions for 20 years. He was known to have had hypertension for years and during the past two years the systolic pressure had been continuously above 200 mm. mercury.

Three days before death he complained of epigastric pain and vomited once. Examination revealed a tender but nonspastic abdomen. He was put to bed but allowed toilet privileges. Forty-eight hours later no improvement was noted and he was transferred to an infirmary ward. On the third day of illness an attendant observed the patient staggering while returning from the toilet. Suddenly he collapsed, fell to the floor, and upon examination was found to be dead.

Pathological Examination. The pericardial cavity contained an estimated 500 c.c. of fluid and fresh blood clot. The heart weighed 540 grams and was the site of an extensive mottled yellow-red soft and friable infarct which involved the lower half of the anterior left ventricular wall and a corresponding area of the interventricular septum which extended around on the posterior wall of the left ventricle for 2 to 3 cm. In the lower half of the infarct near the apex there was an irregular ragged longitudinal linear defect which extended downward and outward from ventricular to pericardial cavity. On the epicardial surface was a thin film of fibrin.

The anterior descending branch of the left coronary artery was the seat of severe sclerosis. One centimeter from its origin there was a segment 3 to 4 mm. long in which the lumen was completely compressed by a fresh hemorrhage into an atherosclerotic plaque. Below this was another segment the lumen of which was occupied by an organizing grayish-brown thrombus. The left circumflex branch showed less marked sclerosis, while the right coronary artery was not significantly involved.

Microscopically the acute infarct was found in myocardium which was the site

of focal scarring. There were large areas of coagulative necrosis peripherally infiltrated by polymorphonuclear leukocytes, most of which had sharply outlined nuclei. Other regions of the infarct chiefly near the endocardial surface showed necrotic polymorphonuclears. Peripherally there were small foci of invasion by young fibroblasts and capillaries in which muscle fibers were in a more advanced stage of dissolution. Only a rare pigmented macrophage was encountered.

Case 2. History. The deceased was a white male of 62 years who had been a patient for 21 years, the mental diagnosis being dementia praecox of paranoid type. Eight months before death a clinical diagnosis of acute myocardial infarction had been made and his name had been placed upon the danger list. Following a period of bed immobilization there was apparent recovery. The heart was considered enlarged and the blood pressure was 160 mm. Hg systolic and 90 mm. diastolic.

Immediately prior to his death the deceased appeared well physically and carried out his usual activities. Suddenly, while walking about on the hospital grounds, he collapsed and fell to the sidewalk, sustaining lacerations of the head. When he was examined by a physician he was found to be dead.

Pathological Examination. The pericardial cavity was distended with freshly clotted blood. The heart weighed 570 grams. Midway between apex and base the lateral wall of the left ventricle was the site of a mottled yellow-red soft and friable infarct 3.5 cm. in diameter. On the underlying endocardium were small recent thrombi, while on the epicardium was a thin layer of fibrin. There was a diagonal linear ventricular defect in the approximate center of the infarct. The defect began posteriorly from the endocardial surface and by thin linear slices was traced anteriorly and upward to its point of exit on the lateral surface of the left ventricle.

The myocardium of the interventricular septum and left ventricular wall near the apex was replaced in large foci by dense cicatrization.

The coronary arteries were the seat of severe arteriosclerosis. The left anterior descending artery showed obliterating disease by continuous hyaline and calcific subintimal plaques. At a point approximately 2 centimeters from its origin the vessel was obliterated by a gray-brown mass. One and one-half centimeters from its origin the lumen of the left circumflex artery appeared completely obliterated by a soft red mass. The right coronary artery showed moderately severe arteriosclerosis and its descending ramus likewise revealed a lumen occupied by a fresh thrombus.

Noncardiac significant abnormalities outside the heart included severe atherosclerosis of the aorta and moderate cerebral arteriosclerosis and arteriolar nephrosclerosis.

Microscopically at the site of rupture there appeared to have been two distinct recent infarcts which occurred in atrophic muscle fibers separated by loose collagen deposit. The first infarct was in a state of recent necrosis and showed minimal infiltration by polymorphonuclear leukocytes. In direct relation there was an abrupt transition to a lesion in which almost all of the myocardium had been removed, its site being occupied by organizing connective tissue containing a few macrophages (figure 1).

Case 3. History. The deceased was a white male of 77 years who had been a patient in a state mental institution for 22 years. The mental diagnosis was alcoholic psychosis with chronic hallucinosis. Eighteen months before death a diagnosis of aortic stenosis had been made by the medical service of the hospital. Somewhat later attacks of syncope associated with a slow pulse occurred and a diagnosis of Adams-Stokes syndrome was made. Fourteen months before death the blood pressure was 200 mm. Hg systolic and 120 mm. diastolic; succeeding readings were similarly elevated.

On the day of death at 5:15 a.m. the deceased fainted while walking to the toilet

and fell to the floor, sustaining a contusion of the left forehead. He was put to bed. In the afternoon there was a slight fever. He died unexpectedly in bed at 4:45 p.m.

Pathological Examination. The pericardial cavity was distended with blood. The heart weighed 460 grams. On the anterior surface over the interventricular septum and about 2 centimeters from the apex there was a slightly curved vertical linear defect with ragged edges 1.5 centimeters in length (figure 2). The anterior wall of the left ventricle and the interventricular septum over an area of 4.5 centimeters in diameter near the apex was thinned, mottled yellow-red, and soft. On the endocardial surface were recent thrombi. Examination by linear slicing showed two irregular ragged tears running through the myocardium in close approximation to each other; they converged outward. The more medial of the two proceeded through

FIG. 1. Photomicrograph taken from region of rupture in case 2. There appear to be infarcts of two distinct ages. In the lower half of the photomicrograph, the heart muscle is the seat of acute necrosis and is invaded by but few polymorphonuclear leukocytes. From this approximately 2 day old infarct there is an abrupt transition to the lesion occupying the upper half of the photograph in which the myocardium has been replaced by organizing and richly vascularized connective tissue. A few macrophages remain. This infarct was judged to be at least 3 weeks old. H & E × 150.

the left lateral margin of the interventricular septum. The subepicardium in relation to the defect was the seat of significant hemorrhage.

Beginning at the apex on the posterior wall of the left ventricle were large foci of dense cicatrization over an area 3.0 centimeters in diameter.

The aortic valve was a rigid non-elastic structure and the thickened, rigid and retracted cusps formed a slit-like orifice 1.2 centimeters long and 2 millimeters wide. There was also a chronic valvulitis of the mitral valve which had not apparently impaired its functional efficiency.

The coronary arteries were the seat of severe arteriosclerosis. The anterior descending branch of the left coronary artery showed severe segmental obstructing sclerosis by hyaline and calcific subintimal plaques. There were two areas in the

FIG. 2. Anterior aspect of the heart in case 3. The site of the rupture on the epicardial surface is located close to the apex on the anterior surface of the heart over the interventricular septum. Note the subepicardial hematoma in relation to the defect.

vessel in which the lumen was obstructed, one by an organizing grayish-brown thrombus and the other by a jelly-like red mass. The right coronary artery was the site of severe arteriosclerosis; its lumen was obstructed by an old thrombus about 4 centimeters from the orifice.

In addition to the findings in the heart there were moderate arteriolar nephrosclerosis and severe atherosclerosis of the aorta.

Microscopically a single recent infarct was observed, in relation to the rupture,

in myocardium which was the site of small focal scars. The infarct showed extensive necrosis and its outer portions were infiltrated with numerous polymorphonuclear leukocytes, most of which were degenerating. Penetrating the infarct at its periphery were occasional blood capillaries and a few fibroblasts.

Case 4. History. The deceased was a white female of 62 years with a mental diagnosis of paranoia. She had been a patient in a mental institution for 12 years. She was moderately obese and showed severe hypertension (250 mm. Hg systolic and 120 mm. diastolic) and moderate cardiac hypertrophy.

The night before death at 7:00 p.m. the patient complained of being abused and persecuted but did not mention physical complaints. Shortly thereafter she was found unconscious. She regained consciousness after the administration of stimulants, then again became unconscious, and died about 13 hours after her original complaint.

Pathological Examination. The heart weighed 420 grams. There was extensive subepicardial hemorrhage over the lower anterior aspect of the left ventricle extending medially to include the anterior surface of the interventricular septum. Slightly to the right of the apex of the left ventricle there was a small irregular defect in the epicardium from which blood could be expressed. Thin linear sections showed the myocardium of the anterior and lateral wall of the apex of the left ventricle to be a mottled gray and yellow, in places hemorrhagic, and extremely friable. Through this infarct there extended a small irregular laceration partially obscured on the endocardial surface by a small friable gray mural thrombus.

The coronary arteries were the seat of severe sclerosis and in the midportion of the circumflex ramus of the right coronary artery there was complete occlusion by a grayish-yellow firm mass. Proximal to this occlusive mass there were two small patent branches. For a short distance distal to the occlusion the artery was represented by a slender fibrous cord. There was severe intimal sclerosis of the left coronary artery between the ostium and its bifurcation. Near the origin of the left descending ramus there was a segment of almost complete occlusion in which the lumen was reduced to less than 1 millimeter in diameter. A segment occluded by grayish-yellow non-calcified material was found in the major oblique branch of the left circumflex artery.

There was moderate arteriolar nephrosclerosis.

Microscopically the margins of the acute myocardial infarct were infiltrated by young granulation tissue, numerous pigment-containing macrophages, some plasma cells, and a few eosinophiles. The central mass of the infarct showed necrosis of the muscle and infiltration with varying numbers of polymorphonuclear leukocytes.

Case 5. History. The deceased, a white female of 67 years, whose mental diagnosis was dementia praecox, hebephrenic type, had been a patient in a mental institution for 35 years. She had been paroled into a family-care home for several years, returning to the hospital at stated intervals for examination. The last routine physical examination revealed an enlarged heart and a blood pressure of 180 mm. Hg systolic and 110 mm. diastolic but no other noteworthy findings.

While in her room at the private home early in the morning she is said to have collapsed and fallen to the floor. She was pronounced dead when a physician arrived.

Pathological Examination. The posterior portion of the pericardial cavity was distended by between 150 and 200 c.c. of dark purple clotted blood and here the subepicardium was the site of a fresh hematoma up to 1 centimeter thick. Thin fibrous adhesions between pericardium and epicardium completely obliterated the pericardial cavity anteriorly. The subepicardial fat was uncommonly thick throughout, measuring 2.5 centimeters thick at the base and 1.5 centimeters at the apex. There was an eccentric hypertrophy of the left auricle and of the right ventricle and auricle. The mitral valve was the seat of an important stenosis. Superimposed upon the auricular

surface of the thickened mitral valve leaflets close to the free edge there was a row of small fresh granular vegetations.

The posterior wall of the left ventricle from apex to base and the posterior part of the interventricular septum were soft, friable, and a mottled yellow-red. On the epicardial surface midway between apex and base were a series of small defects covering an area 2 centimeters in diameter. With appropriate sections multiple ragged and irregular defects were found traversing infarcted myocardium from endocardial to pericardial cavity (figure 3).

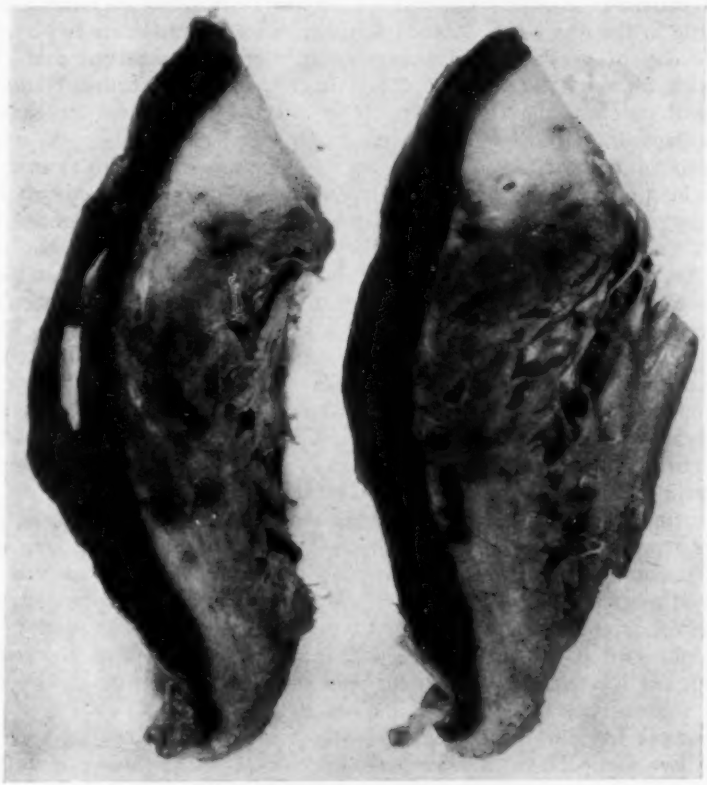

FIG. 3. Longitudinal sections through the posterior wall of the left ventricle (case 5). The upper two-thirds of the ventricular wall is the seat of an acute infarct. Note the large subepicardial hematoma, also the fresh thrombus occupying the lumen of the concentrically narrowed circumflex ramus of the left coronary artery in the photograph to the right.

The coronary arteries were the seat of severe arteriosclerosis and there were continuous hyaline and calcific subintimal patches along their course. The lumen of the anterior descending branch of the left coronary artery showed in its first 3 centimeter segment a lumen completely closed by firm grayish-yellow material. There was similar segmental occlusion in the circumflex ramus which was distal to an occlusion by a gelatinous red mass close to the origin of the vessel. The right coronary artery showed segmental obstructing sclerosis but no occlusion.

Other pathological abnormalities included severe arteriolar nephrosclerosis and ovarian adenofibromata.

Microscopically sections from the posterior wall of the left ventricle showed extensive necrosis of the myocardium. Hemorrhage was rather marked. While erythrocytes were found in dilated venules and capillaries, there was also true extravasation around muscle fibers. These erythrocytes were quite well preserved. Scattered diffusely, and in large numbers throughout, there was infiltration by polymorphonuclear leukocytes many of which were undergoing degeneration. No other cellular exudation was seen.

Case 6. History. The deceased, a white male of 64 years with a mental diagnosis of psychosis associated with organic disease of the central nervous system, had been a patient in a mental hospital for 12 years. Routine physical examinations revealed little in the way of physical abnormalities except moderate hypertension.

On the day of death at 1:30 p.m. a ward attendant observed that the patient appeared sick although he did not complain. A physician ordered transfer to a medical ward. Before the change could be effected the patient developed sudden cyanosis, collapsed, and died at 3:50 p.m.

Pathological Examination. The heart weighed 520 grams. There was a slight but definite bulging of the front of the left ventricle and in its approximate center was a stellate ragged defect measuring 2 centimeters in diameter surrounded by organizing fibrin (figure 4). The walls of the defect were ragged, friable, and blood-stained. The myocardium in the area of bulging was thinned to less than 3 or 4 millimeters and both it and the contiguous portion of the interventricular septum were necrotic, hemorrhagic, and a mottled and laminated yellow-red. The interior of the left ventricle was almost completely occupied by a mural, laminated, adherent, red-gray clot partially covering the site of perforation.

The commissures of the aortic valve were fused and irregular with fibrous and hyaline bands extending from the nodulae of the leaflets to the commissures. The nonaortic mitral cusp was palpably thickened and retracted and the corresponding chordae tendineae were shortened and thickened.

Both coronary ostia were narrowed. In the left descending artery at a point 1.5 centimeters from its origin was the beginning of an 0.5 centimeter long segment in which the lumen was occluded by a firm red clot. Beyond the lumen was obstructed by gray hyaline material and atheroma. The walls were brittle and calcific. The left circumflex artery showed sclerotic narrowing and at one point the lumen was represented by two narrow channels. The right coronary artery showed moderate sclerosis but not to the degree encountered in the left.

There were no other pertinent pathological abnormalities.

Microscopic sections in the region of the rupture showed what appeared to be infarcts of two distinct ages. The first consisted of a large mass of muscle undergoing coagulation necrosis. There was a minimal polymorphonuclear infiltration. From this very recent infarct there was a quite abrupt transition to one in which the heart muscle was completely replaced by well developed collagen. A few fibroblasts and rare macrophages and plasma cells were found at the edge of the acute infarct.

Case 7. History. The deceased was a white male of 64 years who had been a patient in a mental institution for 18 years. The mental diagnosis was dementia praecox, paranoid type. Except for moderate hypertension routine physical examinations had consistently revealed no abnormalities.

On the morning of death he carried through his usual activities of helping about the ward when he stated he felt ill, walked in a staggering manner to his chair about 25 to 30 feet away, collapsed, and was dead upon examination.

Pathological Examination. The heart weighed 440 grams. There was a large 3-centimeters-long irregular vertical defect on the anterior surface of the left ventricle, the lower edge being 2 centimeters above the apex. A probe could be easily passed through the ragged, friable, and blood-stained channel into the endocardial

cavity. There was an extensive, soft, friable, and mottled yellow-red infarct of the lower half of the anterior wall of the left ventricle, the apex, and the contiguous 2 centimeters of the posterior wall together with the interventricular septum. There was slight external bulging of the infarcted left ventricle and in the region of the

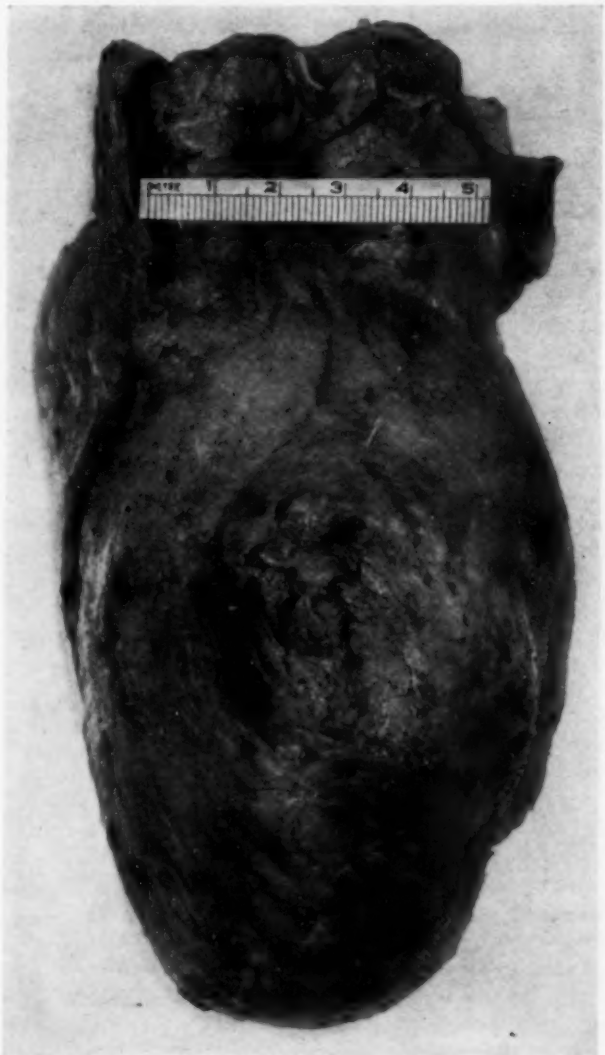

FIG. 4. Large stellate defect on lateral aspect of left ventricle (case 6).

defect the wall measured 5 millimeters in thickness. Continuous with the acute lesion on the posterior wall was an area of slight aneurysmal bulging 3 centimeters in diameter in which the myocardium had been completely replaced by dense scar tissue. In reaction to the acute infarct were epicardial fibrin and endocardial thrombi.

The coronary arteries were the seat of severe sclerosis. The left coronary artery showed severe concentric calcification. The anterior descending ramus showed 3 centimeters from its origin a lumen completely occluded by fairly firm yellow-gray material in a 1 centimeter segment and beyond this the lumen was completely closed by a dark purple-red mass. Two rather large branches arising from the anterior descending artery showed similar recent thrombosis. The right coronary artery at the lateral margin of the heart showed occlusion by a grayish-brown somewhat friable mass. The left circumflex artery was patent but also showed moderately severe disease.

There were also an inconsequential healed mitral and aortic valvulitis and moderate arteriolar nephrosclerosis.

Microscopically the acute infarct occurred in an area in which the muscle fibers were atrophic and separated by thin strains of collagen. There was a large central mass of necrotic muscle and its outer portion was infiltrated by large numbers of necrotic polymorphonuclear leukocytes. At the periphery was minimal invasion by fibroblasts and capillaries. A moderate number of microphages was present.

Case 8. History. The deceased, a white female of 61 years with a mental diagnosis of manic depressive psychosis, depressed type, had been institutionalized for 16 years. During this time routine physical examinations had been essentially negative except for mild chronic hypertension.

Three days before death she stated to her doctor that she had what she thought was indigestion with epigastric pain and distress in her back. She further stated that she frequently had these attacks and would soon be better. No abnormalities being found, she was given phenobarbital for sedation and slept. She continued to be ambulatory and there were no further complaints until three days later when she went to the bathroom and while washing her face suddenly slumped to the floor and died.

Pathological Examination. The pericardial cavity was distended with fresh blood clot. The heart weighed 300 grams. On the anterior wall of the left ventricle two-thirds of the distance from apex to base there was a stellate defect 1.8 centimeters in diameter which communicated with the ventricular cavity by an irregular channel having blood stained and friable walls. The defect was in the approximate center of an acute infarct 5 centimeters in diameter having a mottled yellow-red color. The overlying epicardium had a thin film of fibrin on its surface. There were no other significant abnormalities.

The coronary arteries showed severe obliterating sclerosis but no complete occlusions. The points of extreme narrowing were in the right coronary artery close to its orifice and in the descending ramus of the left coronary also close to its origin. The vessels throughout showed both eccentric and concentric disease with hyaline and calcific plaques predominating.

The kidneys showed moderately severe arteriolar sclerosis.

Microscopically at the site of the rupture the infarcted myocardium was necrotic and infiltrated with many polymorphonuclear leukocytes. Its periphery was invaded by a few capillaries and deeply-basophilic fibroblasts. An occasional fiber had undergone phagocytosis.

Case 9. History. The deceased was a white female of 83 years. Her mental diagnosis was dementia praecox, paranoid type, and she had resided in the hospital for 38 years. Routine physical examination had shown the presence of a loud blowing systolic heart murmur for many years, but there were no other noteworthy physical findings.

The patient resided on a ward for chronic ambulatory patients and on the day of death arose as usual and ate breakfast. After leaving the dining room she sat

on a chair in the day hall and suddenly was observed to slip to the floor. She was dead when a supervisor arrived.

Pathological Examination. The pericardial cavity was occupied by a fresh blood clot. The heart weighed 350 grams. On the anterior surface of the right ventricle close to the interventricular septum and about 2 centimeters from the apex was a linear defect less than 1 centimeter long which communicated with the right ventricular cavity. In relation to this defect was a soft, friable, and mottled yellow-red acute infarct 4 to 5 centimeters in diameter involving both right and left ventricles and intervening septum.

The mitral valve was the site of a severe stenosis.

The coronary arteries showed occluding hyaline and calcific arteriosclerosis with occluding disease in both right and left anterior descending coronary arteries. The latter vessel about 2 centimeters from its origin was obstructed by a recent brownish-red thrombus.

Microscopically sections of the infarcted myocardium showed large areas of necrosis with little or no exudation. In other areas there was infiltration by large numbers of polymorphonuclear leukocytes, most of which were necrotic.

Case 10. History. The deceased was a white female of 68 years who had been a patient in a state hospital for 22 years. Her mental diagnosis was dementia praecox, paranoid type. Five years before death she developed a left hemiplegia from which she made a partial recovery and subsequently became partially ambulatory.

On the day of death, while eating her luncheon, she suddenly became cyanotic, collapsed, and was dead upon examination.

Pathological Examination. The pericardial cavity contained fluid and clotted blood. The heart weighed 340 grams. Immediately adjacent to the interventricular septum close to the apex there was a small vertical linear defect less than 1 centimeter long in the left ventricle which communicated with the ventricular cavity. On the epicardial surface there was a thin soft film of fibrin. In relation to the defect the myocardium over an area roughly 3 centimeters in diameter was soft, friable, and a mottled yellow-red. There were numerous scattered foci of myocardial scarring in the left ventricle and interventricular septum posteriorly near the apex.

The coronary arteries showed severe obstructing arteriosclerosis. At a point 1 centimeter from its origin the lumen of the descending ramus of the left coronary artery was completely closed by a red mass. There was also severe occluding sclerosis in the same vessel and in the right coronary artery with eccentric hyaline and calcified subintimal plaques.

There were moderate arteriolar nephrosclerosis and cerebral arteriosclerosis and an old infarct involving the right internal capsule.

Microscopically the acute myocardial infarct showed simple necrosis of the myocardium and an early reactive phase consisting chiefly of infiltration by polymorphonuclear leukocytes.

Case 11. History. The deceased, a white female of 63 years with a mental diagnosis of dementia praecox, catatonic type, had been a patient in the institution for 13 years. Throughout her hospital stay she had shown severe hypertension and was always obese. There was no history of cardiac failure.

In the afternoon of the day of death she was sitting on a sun-porch together with other patients. It was observed by an attendant that the patient had slumped forward in her chair and when she was placed back in a sitting position it was obvious that she was dead.

Pathological Examination. The pericardial cavity contained from 500 to 700 c.c. of blood clot, mostly fresh. The heart weighed 475 grams. There was an epicardial defect posteriorly on the left ventricle 1.0 centimeter from the apex. The surrounding epicardium was dulled by fibrin. Communication with the ventricular

cavity could be easily demonstrated and the walls of the laceration were friable and blood stained. In relation to the defect there was an acute infarct 4 centimeters in diameter, which was mottled yellowish-red and somewhat thinned. Adherent to the endocardium and partially obscuring the defect were recent thrombi.

The coronary arteries were injected according to the method of Schlesinger and showed extensive obliterating arteriosclerosis with numerous old occlusions chiefly in the anterior descending and left circumflex artery.

The kidneys showed moderate arteriolar sclerosis, and the Circle of Willis was the site of small miliary aneurysms up to 1 millimeter in diameter, none of which showed evidence of rupture.

Microscopically at the site of rupture there appeared to be two distinct infarcts, both of recent origin. The most recent of the two showed simple necrosis and moderate infiltration of its outer part by degenerating polymorphonuclear leukocytes. The second infarct was in immediate relationship to the first and was characterized by an abrupt transition in the type of reaction to one of moderately well advanced organization in which thin strands of collagen were present.

Case 12. History. The deceased was a white female of 72 years who died 23 days after admission to the hospital. Her routine physical examination on admission showed no significant physical abnormalities except for a blood pressure of 175 mm. Hg systolic and 100 mm. diastolic.

On the day of death the deceased was brought to an examining room for a routine pelvic examination. At that time it was noted by a physician that she exhibited some dyspnea. An examination of the heart was made and showed no abnormalities. The pulse was normal. However, the pelvic examination was not performed and the patient was allowed to sit in a chair while the physician examined another patient. Suddenly it was observed that the deceased collapsed; upon examination she was found to be dead.

Pathological Examination. The pericardial cavity was occupied by approximately 500 c.c. of fluid and freshly-clotted blood. There was an area of apical bulging 4.0 centimeters in diameter with thin subepicardial hemorrhagic infiltration. Just above the apex anteriorly there was a ragged stellate defect at the lower margin of which the pericardium was loosely adherent. When thin linear slices were made through the heart it was found that the apical bulging had resulted from aneurysmal dilatation at the seat of an acute myocardial infarct. The ventricular wall varied from 3 to 4 millimeters thick, was soft and friable, mottled yellowish-red, and showed numerous small hemorrhagic foci. The aneurysmal space itself was occupied by endocardial thrombi on the surface of which was fresh blood clot. Continuous with the acute infarct on the anterior left ventricle the myocardium had in great part been replaced by scar tissue.

The coronary arteries were the site of severe arteriosclerosis. The left had a lumen moderately narrowed by atheromatous deposit. The anterior descending artery was completely occluded by an organizing yellowish-gray thrombus over a segment 1.0 centimeter in length beginning at a point 1.5 centimeters from the origin of the vessel. Below the organizing thrombus the artery was completely closed by a firm dark red mass. Two branches of the anterior descending artery were similarly occluded. At a point 1.5 centimeters from its origin the circumflex ramus of the left coronary artery was completely occluded by a firm dark red mass. The right coronary artery was patent for the first 3.0 centimeters although the site of severe sclerosis. Beyond this the vessel was completely occluded by a dark red firm mass.

There was moderate arteriolar nephrosclerosis.

There was a perforated mucocele of the appendix with an extensive pseudomyxomatous peritonitis.

Microscopically the myocardium in the acute infarct was replaced by young

granulation tissue which in some areas showed thin strands of collagen. There were scattered foci of endothelial leukocytes containing brown pigment and moderate infiltration of polymorphonuclears in relation to a central mass of necrotic myocardium.

Case 13. History. The deceased was an epileptic white male of 67 years who had been a patient in state institutions for 40 years. During the last 15 years of life he had shown a hypertension varying from 180 mm. Hg systolic and 100 mm. diastolic to 220 mm. systolic and 120 mm. diastolic.

During the night, 12 hours before death, he had a mild epileptic seizure but was apparently normal thereafter. At noon the following day he suddenly collapsed while in the dining room and was dead upon examination.

Pathological Examination. The pericardial cavity was distended by fresh blood clot. The heart weighed 300 grams. Over the anterior left ventricle midway between apex and base there was a small area of recent pericardial adhesions which partially sealed an epicardial defect. In relation to this fibrinous pericarditis the myocardium was the site of an acute soft and friable infarct which was a mottled yellow-red in color. Through the approximate center of the infarct passed an irregular perforating channel having ragged and blood stained walls.

The coronary arteries showed severe arteriosclerosis with occluding disease in the right and left anterior descending vessels. The latter was also completely occluded by an organizing thrombus close to its origin.

This heart was not studied microscopically.

Case 14. History. The deceased was a white male of 48 years, whose mental diagnosis was manic depressive psychosis, manic type. He had resided in a state hospital for the past four years and his routine physical examinations revealed nothing noteworthy.

The day before death at 6:30 a.m. he complained of a sharp pain in his chest. He was given gr. ¼ of morphine and removed to a medical ward. On examination the temperature was found to be 99.6° F., and the patient was irritable in manner, gagging but not vomiting. The pulse was 64 per minute. He slept in naps during the afternoon and night and the following morning felt better. At 7:00 a.m. he had taken fluids. He was seen by a physician at 9:00 a.m. and looked better. At 10:30 a.m. he got out of bed and walked to the bathroom. Two other patients stated that he slumped to the floor and collapsed after walking two steps. A physician pronounced death at 10:40 a.m.

Pathological Examination. The pericardial cavity was occupied by blood clot. The heart weighed 360 grams. Midway between apex and base over the left ventricle there was a ragged 0.8×0.3 centimeter defect which communicated with the left ventricular cavity. Above this perforation there was a slightly smaller defect which was also complete and communicated with the ventricular cavity. The walls of both defects were ragged, friable, and blood stained. The surrounding epicardium was covered with fibrin. Over an area approximately 5.0 centimeters in diameter the myocardium was the site of an acute infarction and was soft, friable, slightly thinned, and a mottled reddish-yellow with numerous hemorrhagic foci.

The coronary arteries showed extensive arteriosclerosis but no complete occlusion. There was severe obliterating disease by eccentric hyaline and calcific plaques in the descending and circumflex rami of the left coronary artery.

Microscopically there was seen extensive infiltration of necrotic myocardium by polymorphonuclear leukocytes, most of which were necrotic. There were occasional pigment-containing phagocytes and a minimal attempt at repair by peripherally invading young granulation tissue.

Case 15. History. The deceased was a white male of 75 years who had been a patient at the mental institution for four and a half years. The mental diagnosis was

senile psychosis, paranoid type. Routine physical examinations showed chronic hypertension and cardiac hypertrophy.

Three days before death he suddenly collapsed while at supper. Approximately 10 minutes later he appeared resting comfortably. When questioned by a physician he complained of pain in the umbilical region extending downward into the right lower quadrant. Examination of the abdomen revealed no abnormalities. The pulse was said to have been weak but examination of the heart revealed no abnormalities. Subsequently he appeared in no discomfort and was up and about. On the day of death, three days later, while at the cafeteria, he was observed suddenly to become cyanotic and to fall to the floor. He was dead when examined.

Pathological Examination. The pericardial cavity contained an estimated 500 to 700 c.c. of fresh blood clot. The heart weighed 500 grams. On the back of the left ventricle midway between apex and base and about 1.5 centimeters from the interventricular septum there was a slightly diagonal vertical defect 1.5 centimeters long which communicated directly with the left ventricular cavity. The walls of the defect were friable, soft, and blood stained. The perforation was in the approximate center of the large (6.0 centimeters in diameter) infarct showing slightly thinned, soft, and friable muscle discolored a mottled yellow-red. There were small foci of hemorrhage scattered throughout.

The coronary arteries were injected according to the method of Schlesinger and were found to have been the site of severe arteriosclerosis. In the circumflex ramus of the left coronary artery there were recently occluded segments and in one place the lumen was compressed by hemorrhage into an atherosclerotic plaque. The right coronary and the descending ramus of the left showed segments in which the lumina were severely narrowed.

There was severe arteriosclerosis of the aorta and cerebral arteries. The kidneys showed moderate arteriolar nephrosclerosis.

Microscopically there was a large central area of necrotic myocardium with little exudative reaction. The periphery of the lesion was extensively infiltrated by necrotic polymorphonuclear leukocytes. The infarct occurred in muscle the site of small foci of scarring.

Case 16. History. The deceased, a white male of 66 years, with a mental diagnosis of paranoia, had been a patient at the mental institution for about six months. Physically he was moderately obese, and the blood pressure was 210 mm. Hg systolic and 120 mm. diastolic. His general health seemed good and he never complained.

While on the hospital grounds walking from one building to another he suddenly collapsed and in 15 minutes was dead.

Pathological Examination. The pericardial cavity was occupied by fresh blood clot. The heart weighed 510 grams. On the anterior wall of the heart, slightly to the left of the interventricular septum there was a large linear vertical defect 2.5 centimeters long which gaped at its mouth to 0.5 centimeter. The external defect was found to communicate with the left ventricular cavity by means of a ragged blood stained channel. In relation to the perforation the myocardium was the site of an acute infarct over an area roughly 5.0 centimeters in diameter. The interventricular septum was involved in the process. The infarcted myocardium was soft, friable, slightly thinned, and a mottled yellow-red.

The descending and circumflex rami of the left coronary artery showed occluding arteriosclerosis, most marked in the former branch. The right coronary artery was less severely involved.

Microscopically the infarct in relation to the rupture showed a moderately advanced stage in the removal of muscle fibers and replacement by granulation tissue containing a small amount of collagen. There were considerable numbers of pig-

ment-containing macrophages and varying numbers of polymorphonuclear leukocytes, plasma cells, and eosinophiles. The former were found in a centrally located mass of necrotic muscle.

Discussion

Although spontaneous rupture of the heart through a fresh myocardial infarct is an occasional finding by the coroner in his postmortem examination of individuals who die unexpectedly, as noted by Martland who found 42 such cases (13.8 per cent) among 304 instances of coronary occlusion in a series of 2,000 autopsies,[2] the percentage of ventricular ruptures in the present series (73 per cent) is by far the highest that we have known about. It is especially interesting and instructive to compare it with the percentages of cardiac ruptures encountered in the wards of general hospitals, for example, 8 per cent (72 cases among 865 of unhealed myocardial infarcts) at the Los Angeles County Hospital[3] and 9.5 per cent (10 cases among 105 of fresh myocardial infarcts) at the Massachusetts General Hospital.[4] As a rule the cases found in the general hospitals entered the wards with the diagnosis already made and so, with their own intelligent and vital cooperation, were treated by complete bed rest and other necessary measures in the most approved manner; despite that fact there were hearts that ruptured, owing in the main to the severity of the disease, perhaps an almost irreducible minimum.

Apropos of the general subject of medical diagnosis and care in the mentally ill, it should be observed that difficulties are encountered not ordinarily present in the general community. Frequently the psychotic individual does not complain even though he is desperately sick. Particularly is this so in the chronic mental patient who has deteriorated intellectually. It will be observed that this was the type of individual which predominated in the present series. It has been our experience that many mentally ill persons do not complain even though they are the victims of severe degenerative or infectious disease. Moreover, even though they do complain, their symptoms are likely to be so bizarre and distorted that their significance is likely to go unrecognized. Although mental institutions are fully aware of these difficulties and train their ward personnel to detect and report seemingly insignificant behavior changes in their charges, it remains a fact, however, that all too frequently the physician is confronted with the task of making a medical diagnosis by objective findings alone.

Summary and Conclusions

1. In a series of 115 consecutive autopsies of patients who died suddenly or unexpectedly in Massachusetts Mental Institutions 16, or 73 per cent, of a total of 22 cases of acute myocardial infarction showed cardiac tamponade due to rupture of the heart wall at the site of the recent infarct.

Cardiac rupture was not found in any of the 25 cases in the same series with healed infarct only.

2. The psychiatric diagnoses were dementia praecox in six cases, manic depressive psychosis in two, paranoia in two, alcoholic psychosis in one, senile psychosis in one, epilepsy in one, imbecility in one, organic disease of the central nervous system in one, and undiagnosed in one.

3. The mean age of the 16 persons whose hearts ruptured was 66.5 years, slightly less than one year older than the average age in Friedman and White's series.[4] Ten were males and six females.

4. Fourteen of the 16 patients had shown a moderate to severe hypertension in past years. In only one case was there a definite history of angina pectoris.

5. Ten of the patients were ambulatory and in apparent good health before their sudden collapse and death. Four patients had complained mildly and two of these received partial bed rest. The remaining two persons were incapacitated during the approximate last 12 hours of life incident to the development of an extensive subepicardial hematoma. A definite antemortem diagnosis of myocardial infarction or cardiac rupture was not made in any of the cases.

6. The acute myocardial infarct, through which the rupture occurred, was located in the left ventricle in eight instances (anterior wall five, posterior wall two, lateral wall one), both left ventricle and interventricular septum were involved in seven cases, and in the sixteenth case both ventricles and the intervening septum were included. Early fibrinous pericarditis was present in 10 and endocardial thrombosis in nine. The ruptures involved the left ventricular wall in 15 cases and the right in one.

7. The estimated age of the responsible infarct was two to four days in six cases, two to six days in three cases, one to two weeks in four cases, two to three weeks in two cases, and not stated in the remaining case.

8. This experience, in contrast to that in ordinary medical practice where it is possible to make early diagnoses and to institute adequate treatment, strongly supports the present approved therapy of bed rest during the first three weeks after the onset of acute myocardial infarction.

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KEROSENE INTOXICATION *

By W. B. Deichmann, Ph.D., K. V. Kitzmiller, M.D., F.A.C.P., S. Witherup, B.S., and Ralph Johansmann, M.D.,
Cincinnati, Ohio

Kerosene is a hydrocarbon complex, derived from crude oil or petroleum, used essentially for illuminating and heating purposes. It is composed of fractions of high boiling point (initial 200–350° F., final 500–600° F.) and relatively low volatility, and differs according to the source and consequent composition of the crude oil stocks. These are essentially asphaltic and paraffin-base derivatives, the former containing aromatic and highly unsaturated hydrocarbons. Refining processes usually leave traces of impurities in the finished product. These may be sulfur and nitrogen compounds, caustic alkali, alkaline plumbite solution, organic solvents and adsorbents such as fuller's earth. The kerosenes referred to in the experimental observations reported herein (table 1), were obtained from mid-

Table I

Comparison of the Toxicity of Various Brands of Kerosene Administered Orally in One Dose to Rabbits
The dose in each instance was 28 ml./kg.

Source of Kerosene	Number of Rabbits Used	Per Cent of Deaths
Pure Oil Co.	20	50
Eureka Oil Co.	6	66
Tower Oil Co.	6	0
Re-Go Oil Co.	6	50
The Texas Co.	6	66
White Rose	6	50
Socony-Vacuum Oil Co.	6	17
Sinclair Refining Co.	6	33
Sinclair Refining Co.*	6	33
Shell Oil Co.	6	50
Standard Oil Co.	6	17
Sun Oil Co.	6	50
Gulf Oil Corp.	6	17
Commercial Solvents Corp.*	6	0

* These kerosenes were highly purified for use as bases for insecticide sprays.

continent or Pennsylvania crude oil and were composed primarily of paraffin hydrocarbons and contained only small amounts of naphthenic, aromatic and olefinic compounds.

Etiology

In the petroleum industry kerosene intoxication has little importance. Outside the industry it occurs frequently as the result of accidental ingestion usually by infants and children whose ages range from 10 months to three

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From the Kettering Laboratory of Applied Physiology, and Department of Pathology, Children's Hospital, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

years. These cases of poisoning result from careless household use and storage of the compound and often occur because it is left in glasses, cups and bottles commonly used for milk and other beverages, and placed within the reach of small children. Numerous fatal cases have been recorded among infants and children as the result of swallowing small amounts of kerosene.[1, 2, 3, 4, 5, 6, 7, 8] Among adults, however, susceptibility is apparently much less since no fatal cases are on record despite reports of the ingestion of considerable quantities.[5]

Acute Poisoning

Symptoms and Clinical Findings. The clinical picture of kerosene intoxication is characterized by both immediate and delayed effects. In the former the irritant action of the liquid is evidenced by burning of the mouth and throat, spasm of the glottis, coughing and choking, substernal and epigastric pain and frequent vomiting. Shortly following absorption, evidence of cerebral depression is manifested by drowsiness, collapse, muscular twitching and coma, usually associated with feeble, rapid pulse, accelerated respiration and moderately elevated temperature. When death is delayed for several days, there is evidence of myocardial insufficiency, hepatic and renal damage, and pneumonia usually terminates the picture. The following case report illustrates the essential points in acute poisoning.

Case Report

A one-year-old white male child previously in good health and with no history of former illnesses drank a mouthful of kerosene from a bottle found on the floor of his home. Coughing ensued immediately. The mother gave the child soda water by mouth and took him to a physician's office, arriving within 10 minutes. There the stomach was lavaged with two quarts of baking-soda solution. The child was then sent to the Children's Hospital and arrived there in a state of collapse 50 minutes after drinking the fluid.

Physical Examination. The child was well developed and well nourished but moribund and cyanotic. The mucous membrane of the nose was congested, the throat intensely reddened, and a distinct odor of kerosene was detected on the breath. The pupils were regular and equal, but reacted sluggishly to light. The heart sounds were weak and rapid. There were no murmurs. Respiration was irregular and gasping. There was impaired resonance over the entire thorax, and many coarse râles and rhonchi were heard throughout all lung fields. The abdomen was distended. The extremities were cold, and the reflexes hypoactive.

Course in Hospital. Coramine was administered immediately on admission and within 15 minutes the child was placed in an oxygen tent. Hot water bottles and warm blankets were applied and a continuous infusion of 5 per cent glucose was given intravenously. Suction applied to the throat obtained a moderate amount of mucus. Within two hours after admission the pulse rate was 136, the respiratory rate had risen to 80, and the temperature was 102.2° F. Again suction to the throat recovered a large amount of thick white mucus mixed with bright red blood. Vomiting occurred and the vomitus, which was small in amount, consisted of thick mucus possessing a strong odor of kerosene. The pulse and respiratory rates remained rapid, but for a few hours the cyanosis lessened and almost disappeared, and the child's condition

seemed somewhat improved. The lungs, however, remained full of coarse râles and rhonchi. Sodium luminal was administered to allay restlessness. Six hours after admission the child's condition became worse, cyanosis returned, and throughout the ensuing two hours became progressively more intense. Respirations soon became very shallow and the pulse very weak and barely palpable. Caffein sodium benzoate and adrenalin chloride were administered to no avail and the child died eight hours after admission to the hospital and within nine hours after ingestion of the kerosene. No laboratory examinations were made.

Necropsy Findings. Necropsy was performed eight hours after death.

Gross Examination. The body, 73 cm. in length, was that of a well developed, well nourished, white, one-year-old male infant. The pleurae were smooth and moist, and approximately 50 c.c. of clear fluid were present in the left pleural cavity. The lungs were large and heavy and the pleural surfaces were generally dark reddish-blue, but were spotted along the anterior borders by a few small light pink areas and a few slightly raised emphysematous blebs. Sections of the lung revealed moderately wet, uniformly reddened, fairly firm and practically air-free tissue from which a frothy fluid was expressed. A strong odor of kerosene emanated from the pulmonary tissue. The tracheobronchial tree was lined by a pink to slightly red mucosa without ulceration and was filled with frothy pink fluid. Similar fluid filled the nose and mouth.

The lining of the esophagus was smooth, light reddish-blue and without ulceration. The stomach was distended with gas and contained a small amount of tan mucus having a distinct odor of kerosene. The gastric mucosa was without ulceration but that of the fundus was spotted by several small light red areas not more than 2 mm. in diameter. Peyer's patches were moderately prominent in the ileum, pale gray, and speckled with numerous tiny white spots. Tiny 1 mm. mucosal erosions were noted overlying many of the prominent solitary lymph nodules of the colon. Numerous moderately enlarged light tan lymph nodes were contained in the mesentery.

The liver was slightly enlarged and consisted of slightly swollen, slightly congested, light tan tissue mottled with small areas of yellow. An odor of kerosene was detected in the tissue.

The splenic pulp was light red and rather mushy and the gray follicles were prominent.

The cortex of the kidneys was light tan, swollen and slightly congested. The urinary bladder was moderately distended with clear urine which was free from the odor of kerosene. The cortex and medulla of the suprarenal glands were thin but not otherwise remarkable.

There were no abnormalities of the heart other than slight dilatation of the chambers.

Permission was not extended for examination of the central nervous system.

Microscopic Examination. Sections representing all lobes of the lungs showed edema, marked hyperemia, some capillary endothelial swelling, focal areas of acute interstitial inflammation, small hemorrhages, and exudate consisting of inflammatory cells in the alveoli (figures 1 and 2). The inflammatory exudate varied somewhat in quantity in various areas but in general consisted of fluid, fibrin, polymorphonuclear leukocytes and mononuclear leukocytes. An occasional foreign body giant cell was present. In some areas the fibrin appeared condensed in a thick red to reddish-blue membrane which was plastered against the alveolar lining (figure 3). Some of the smaller bronchi and bronchioles were partially filled with exudate but presented no evidence of inflammation of the mucosa or supporting tissue. Some, having an intact mucosa, were diffusely infiltrated by inflammatory cells; others showed necrosis of the epithelium with an associated intense inflammatory reaction (figures 1 and 4). Although the alveolar exudate was generalized, it was more pronounced in some of

FIG. 1. Section from the lung of a child who died nine hours after swallowing kerosene. Note marked hyperemia, edema and interstitial and alveolar acute inflammatory exudate.

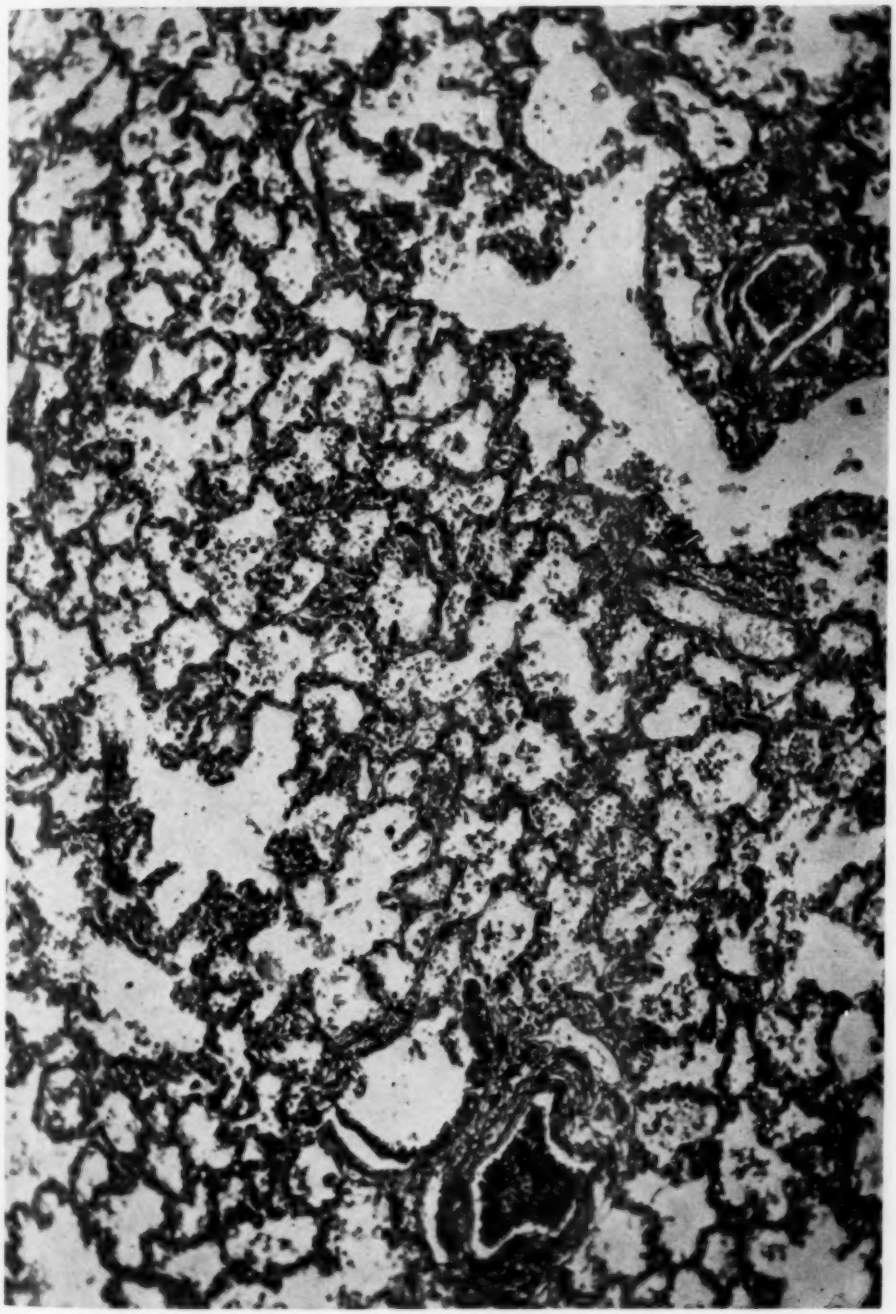

FIG. 2. Section from the lung of a child who died nine hours after swallowing kerosene. Note vascular engorgement and fibrino-cellular exudate in alveoli.

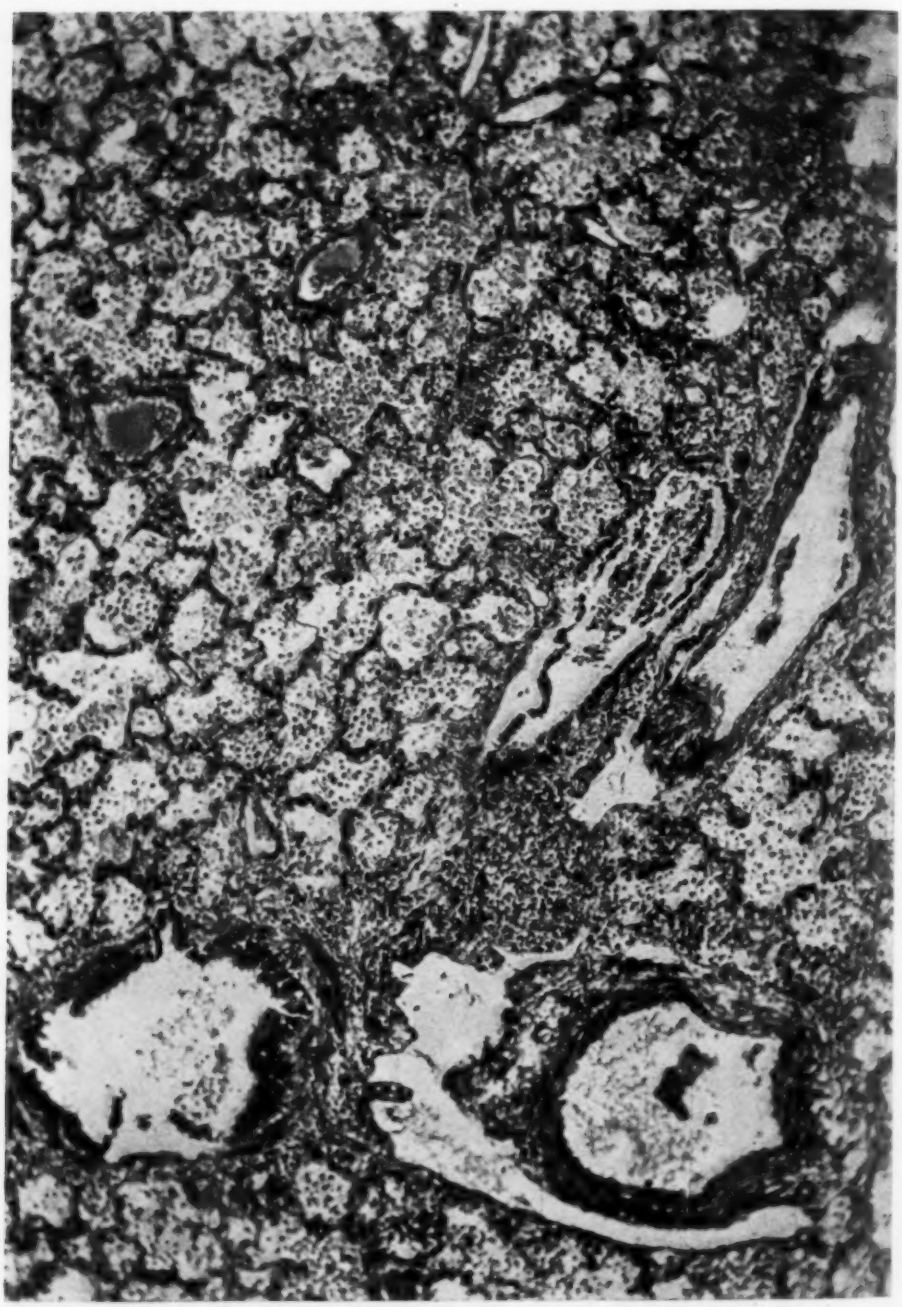

FIG. 3. Section from the lung of a child who died nine hours after swallowing kerosene. Note evidence of vascular and bronchial injury and well defined fibrino-cellular exudate in alveoli.

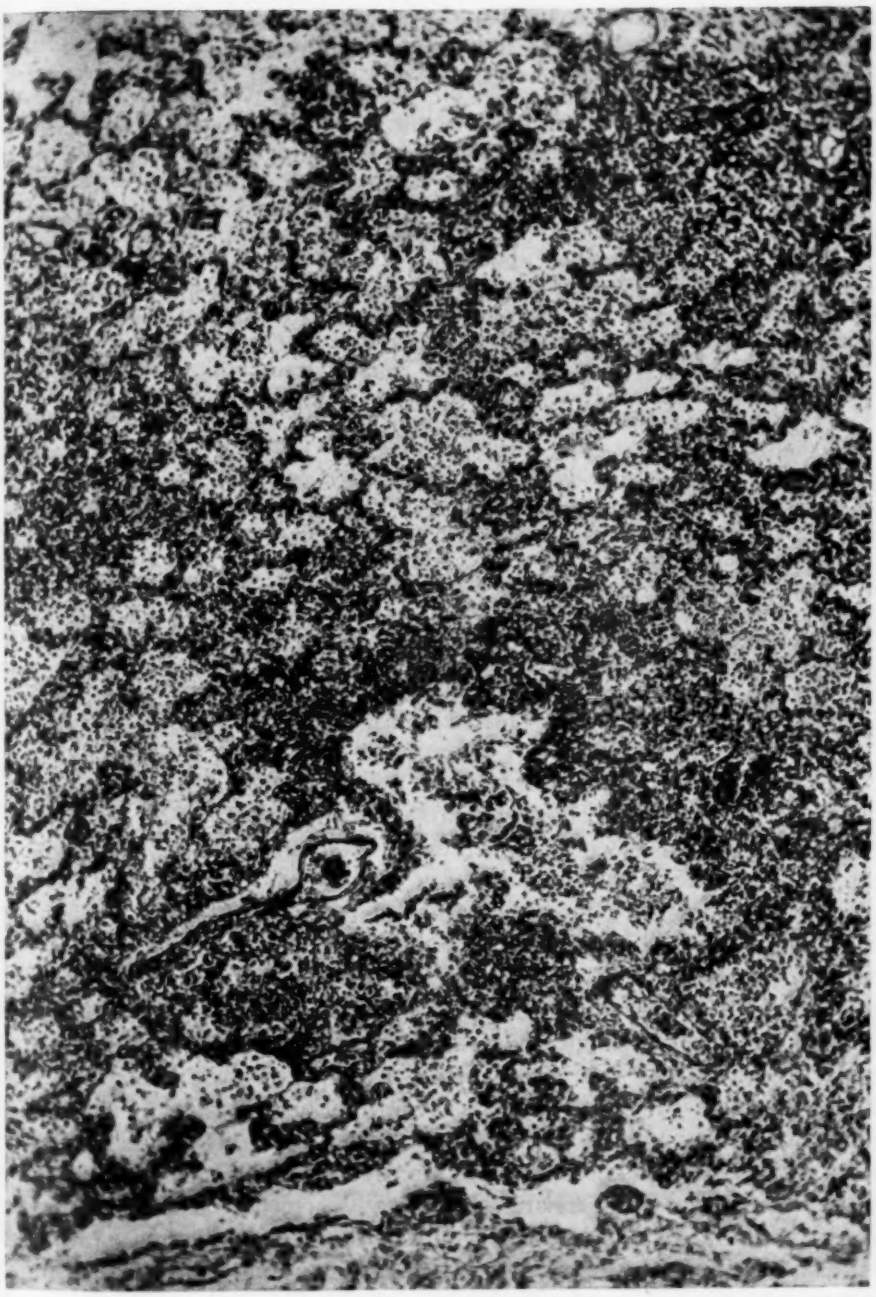

FIG. 4. Section from the lung of a child who died nine hours after swallowing kerosene. Note more intense acute inflammatory reaction in the parenchyma and ulceration of the bronchial wall with loss of epithelium and marked inflammatory cellular infiltration.

the lobules in which the small bronchi and bronchioles presented evidence of ulceration (figures 1 and 4). The epithelium of the trachea and large bronchi was denuded in areas, leaving a bare basement membrane. The lamina propria was moderately congested and contained an occasional petechial hemorrhage. However, there was no evidence of cellular inflammatory reaction. The bronchial lymph nodes were swollen, congested and infiltrated by inflammatory cells, but other lymph nodes throughout the body, notably those in the mesentery, presented only rarefaction of the germinal centers.

The esophagus was essentially normal except for marked congestion of the mucosa and submucosa. The gastric mucosa was intact and, except for moderate congestion, appeared normal. The lymphoid tissue of the small intestine was hyperplastic and slight mononuclear leukocytic infiltration was noted in the tips of some of the villi. There was beginning follicular rarefaction of the solitary lymph nodules of the colon and denudation of the overlying mucosa. Small foci of mononuclear and polymorphonuclear leukocytic exudate were present in the mucosa with extension in a few areas into the submucous layer. In the latter areas the capillaries were congested and collared by leukocytes, and the capillary endothelium was swollen.

In the liver there was congestion of the sinusoids, slight swelling of the Kupffer cells and slight fatty infiltration in the peripheral portions of the lobules. The spleen was congested. Congestion, slight swelling of the epithelial cells of the convoluted tubules, and precipitation of granular material in the convoluted tubules were the principal changes noted in the kidneys. In the heart there was general congestion and small areas were seen in which the muscle fibers were vacuolated and fragmented with loss of cross striations. The bone marrow appeared normal.

Pathologic Diagnoses. Acute pulmonary congestion and edema, acute diffuse confluent lobular pneumonia, acute bronchitis, acute bronchial lymphadenitis, slight toxic nephrosis and myocardosis, slight fatty infiltration of the liver, mucosal erosions of the colon, passive congestion of the abdominal viscera.

Discussion

In the case here described the fatal outcome occurred as the result of rapid absorption of the ingested kerosene from the gastroenteric tract and its passage by way of the blood stream to the organs and tissues of the body, notably to the lungs. Here, as a result of its two-fold action, vascular and parenchymal damage occurred followed by the development of hemorrhagic stasis, edema and diffuse lobular pneumonia. In kerosene poisoning it is undoubtedly true that the bronchi, bronchioles and alveoli contain kerosene both as a result of its hematogenous transfer, and also, in some instances, as a result of aspiration. Pulmonary retention of the kerosene occurs because of its low volatility, for it does not pass from the lungs readily, if at all, in the expired air. As a result of this fact, which has been established experimentally, increased pulmonary ventilation has no beneficial effect other than to prevent anoxia or eliminate it if already present. Thus, the kerosene present in the lungs remains there until removed by other mechanisms and acts as a continuing injurious agent, thereby increasing the degree of inflammatory response and greatly diminishing the likelihood that pulmonary damage will be minimal.

The probability of aspiration of kerosene in regurgitated gastric fluid cannot be denied in most cases of clinical poisoning, but it makes little dif-

ference in the over-all pathologic picture except to add to the damage already present in any serious case of poisoning. Although the development of acute necrotizing lesions in scattered small bronchi is suggestive of direct exposure to the irritant, the presence of these presumably characteristic lesions does not prove conclusively that the irritant has been aspirated, since very similar pathologic changes can be produced in the lungs of experimental animals in which the possibility of aspiration has been completely removed.

Pathogenesis

The pathologic changes caused by kerosene are the result of its irritant action. Locally, whether on the skin or the mucous membranes of the oral cavity, the respiratory or the gastroenteric tract, it is capable of producing severe corrosive lesions accompanied by local exudative inflammatory phenomena conditioned by the physiologic characteristics of the surfaces involved. These lesions may be mild or severe depending on the degree of dilution of the kerosene and the length of time it is permitted to remain in contact with the tissues. Upon its removal healing occurs with complete restoration to normal if the damage has not been too severe. If it has been severe, fibrosis and scarring occur and healing is long delayed and frequently complicated by secondary pyogenic infections.

Following absorption there is evidence of generalized toxemia with depressant effects on the central nervous system as well as on the other organs of the body, notably the liver, kidney and heart muscle. These changes, of course, vary with the degree of exposure and if not too severe may be completely reversible. Vascular damage consisting primarily of cloudy swelling of the intima, media and adventitia, perivascular fluid extravasation and occasional collections of monocytes and lymphocytes in the perivascular spaces, constitutes the essential lesion in all the viscera. Albuminous degeneration and frequent coagulation necrosis occur in the myocardium, liver and kidney. The spleen is acutely congested, contains many phagocytic macrophages and much free hemosiderin. The reticulo-endothelial cells are hyperplastic and the follicles large and active. The most interesting pathologic picture is seen in the lungs in severely poisoned cases. It has long been the accepted opinion that pulmonary changes occur only when kerosene is aspirated,[1, 2, 3, 4, 5, 6] and just recently this opinion has been re-affirmed by Lesser, Weens and McKey[8] following a clinical, roentgenographic and experimental study of the pulmonary manifestations after ingestion and aspiration of kerosene. These authors conclude that "the pulmonary changes are brought about by aspiration of kerosene into the respiratory tract and are not the result of absorption from the gastrointestinal tract with subsequent excretion into the lungs."[8]

It is the primary purpose of this paper to refute these statements and to demonstrate the two-fold nature of the lung injury in kerosene intoxication.

It is not uncommon in toxicologic studies to have pulmonary damage

from excretion of blood-borne materials following their ingestion, cutaneous application, or parenteral injection.[9, 10]

Moon [11] discusses lung injury with the formation of pulmonary edema from increased vascular permeability induced in a variety of ways, principally by injection of foreign protein, histamine, bile salts, and peptone, and by drug poisoning, burns, intestinal obstruction, and by the introduction of muscle substance intraperitoneally. From a review of the experimental work cited below having to do with the toxicology and pathogenesis of kerosene poisoning it becomes apparent that pulmonary damage of this same general type does occur in kerosene intoxication.

Toxicology, Experimental Pathology

Oral Administration. In experimental animals large oral doses of kerosene caused increased respiration, hypoglycemia, mild hyperpyrexia (figure 5), progressive muscular weakness and tremor, followed by marked dyspnea,

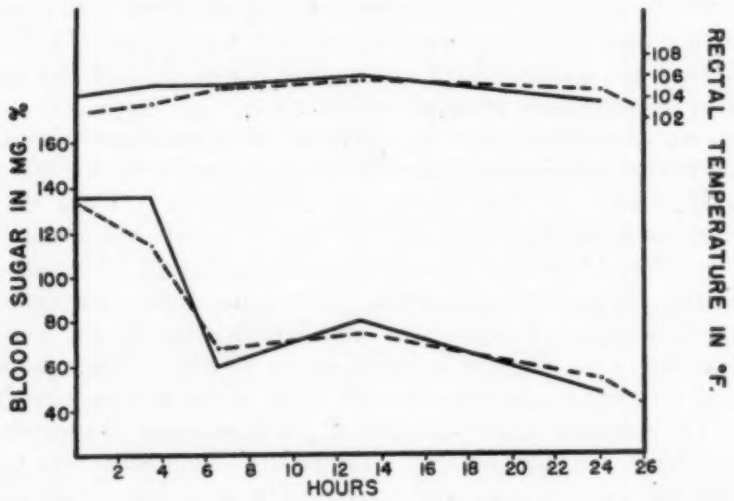

Fig. 5. Effect of a lethal oral dose of kerosene on rectal temperature and blood sugar of two rabbits.

hypopyrexia, and coma frequently resulting in death. Only faint traces of kerosene appear in the exhaled air. The lethal dose (LD_{50}) of one sample of kerosene was 28.4 ml. per kilogram for adult rabbits, and 20.4 ml. per kilogram for adult guinea pigs. The compound was even less toxic for adult rats, a dose of 28 ml. per kilogram killing only four of 15 animals. Kerosene obtained from other sources displayed approximately the same degree of toxicity. Tables 1 and 2 summarize the results on these animals.

An experiment was carried out to determine whether or not young animals of other species show the great susceptibility that appears to exist in the case of small children as compared to human adults. The results show

TABLE II

The Toxicity of One Brand of Kerosene When Administered Orally in One Dose to Adult Rabbits and Guinea Pigs

Number of Animals Employed	Dose ml/kg	Per Cent of Deaths	Time until Death	LD_{50}
		Rabbits		
10	10.0	0		
10	16.0	30	12 hrs. to 6 days	*28.35 ml./kg.*
10	24.0	40	2 to 5 days	
10	36.0	60	2 to 10 days	
		Guinea Pigs		
10	4.7	10	3 days	
10	7.0	10	3 days	
10	10.0	10	3 days	*20.38 ml./kg.*
10	16.0	30	1 to 8 hours	
10	24.0	70	1 hr. to 3 days	

that young rats are highly susceptible, the lethal dose for 10-day-old animals being approximately 7 ml. per kilogram (table 3). However, three-week-old rabbits were only little more susceptible than adult rabbits.

Skin Application. Three milliliters per kilogram applied to the skin of rabbits daily for six consecutive days, without employing a bandage, caused

TABLE III

The Toxicity of Orally Administered Kerosene for Rats of Different Ages

Number of Rats Employed	Age	Dose ml/kg	Per Cent of Deaths	Time until Death
15	adult	28	27	1 to 3 days
15	5 weeks	28	66	1 to 4 days
15	10 days	28	100	1 to 3 days
10	10 days	20	100	1 to 3 days
15	10 days	10	100	2 to 4 days
10	10 days	7	50	3 to 7 days
10	10 days	5	40	3 to 7 days

some local loss of hair and scaling and cracking of the epidermis, but did not produce evidence of systemic illness.

Intravenous and Intraperitoneal injection. The toxicity of kerosene when injected intravenously into rabbits was determined because of the desirability of using this liquid or one with similar properties, as a solvent for certain solid substances that were to be administered in this fashion. The dose of kerosene was injected into the marginal ear vein at a rate of 0.2 ml. per minute. Signs of poisoning resembled those seen after oral administration. The lethal dose is approximately 0.18 ml. per kilogram (table 4). The intraperitoneal injections were made for the purpose of permitting absorption to

occur over this large surface while preventing all possibility of intrapulmonary aspiration. The lethal dose (LD_{50}) following this means of administration was 6.6 ml. per kilogram (table 5).

Inhalation. Inhalation exposures were not carried out with animals because the low vapor pressure of kerosene makes poisoning by inhalation unlikely.

TABLE IV

The Toxicity of Kerosene When Administered Intravenously to Rabbits

Number of Animals Employed	Dose ml/kg	Per Cent of Deaths	Time until Death
4	0.12	0	
4	0.18	50	5 hrs. to 2 days
4	0.28	75	2 hrs. to 3 days
4	0.42	100	1 hr. to 4 days

Pulmonary Lesions. The pathologic changes produced in the lungs were of the same general character whether administration of kerosene was by stomach tube or by intraperitoneal injection.

In order to demonstrate the nature of the pulmonary injury, lethal doses of kerosene were injected intraperitoneally in a series of rabbits. These died 7, 9, 11, 13, 24, 30 and 50 hours after treatment. Gross and microscopic examinations were carried out on the lungs of all the animals. The pathologic findings were very similar in all instances except that the lesions were

TABLE V

The Toxicity of One Brand of Kerosene When Administered Intraperitoneally in One Dose to Adult Rabbits

Number of Animals Employed	Dose ml/kg	Per Cent of Deaths	Time until Death	LD_{50}
10	3.2	0		
10	4.7	40	10 to 13 hours	
10	7.0	60	10 to 20 hours	
10	10.0	80	6 to 18 hours	*6.6 ml./kg.*
10	16.0	80	6 to 19 hours	
10	24.0	100	7 to 20 hours	

more advanced in those animals in which a greater time interval had elapsed between treatment and death.

On gross examination the lungs were voluminous. The tense, yellowish pink and dark pinkish red pleural surfaces were moist, smooth and glistening, and the upper lobes were marked posteriorly with dark red subpleural hemorrhagic extravasations. Tremendous emphysema was seen everywhere in the crepitant parenchyma, causing irregularity of the pleural surfaces. On section the cut surfaces were covered with frothy serosanguineous fluid which oozed from the parenchyma, and filled the bronchi and trachea (figure 6).

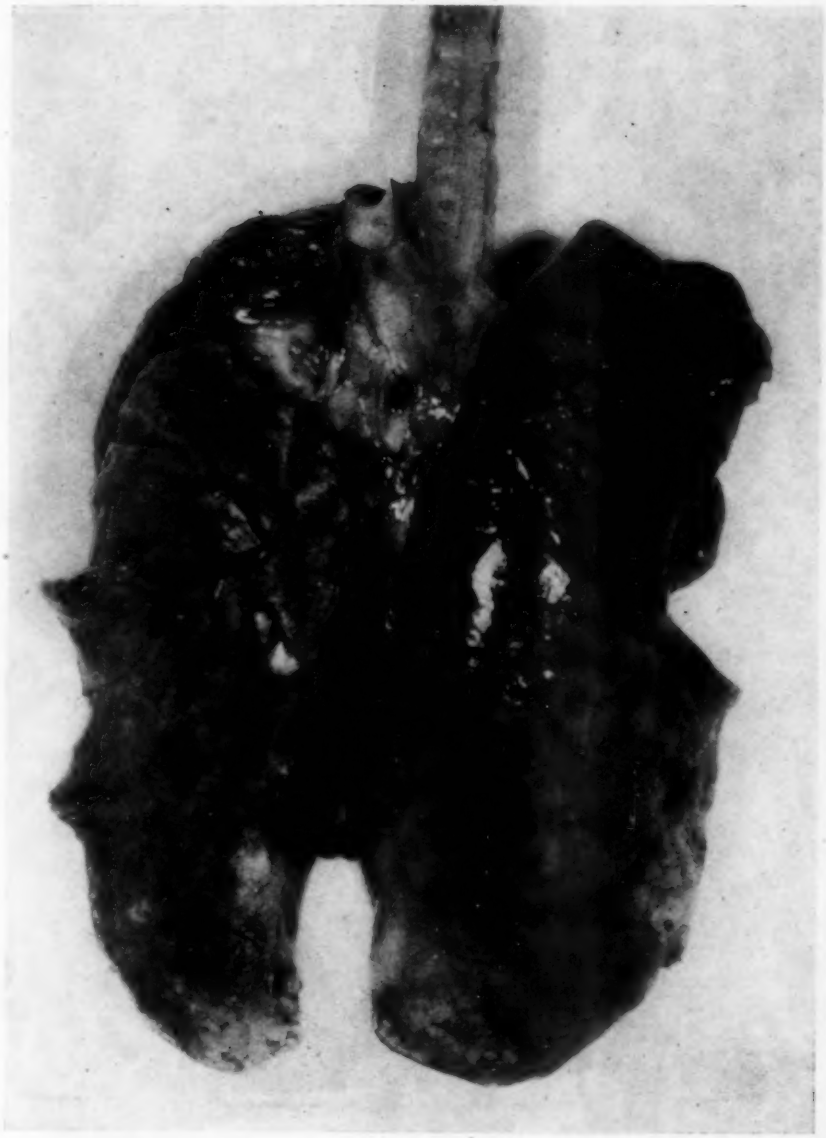

FIG. 6. Lungs of rabbit which received a lethal oral dose of kerosene demonstrating the pathologic changes as described in the text.

Alteration in the pulmonary circulation with evidence of damage to the vessel walls was the most uniform and consistent finding on microscopic examination. The vessels were acutely congested with engorgement of the venules and capillaries, and frequent hemorrhagic extravasation into the interstitial tissue and alveoli (figure 7). Cloudy swelling occurred in all coats of the vessels, and very frequently there was edema of the adventitia

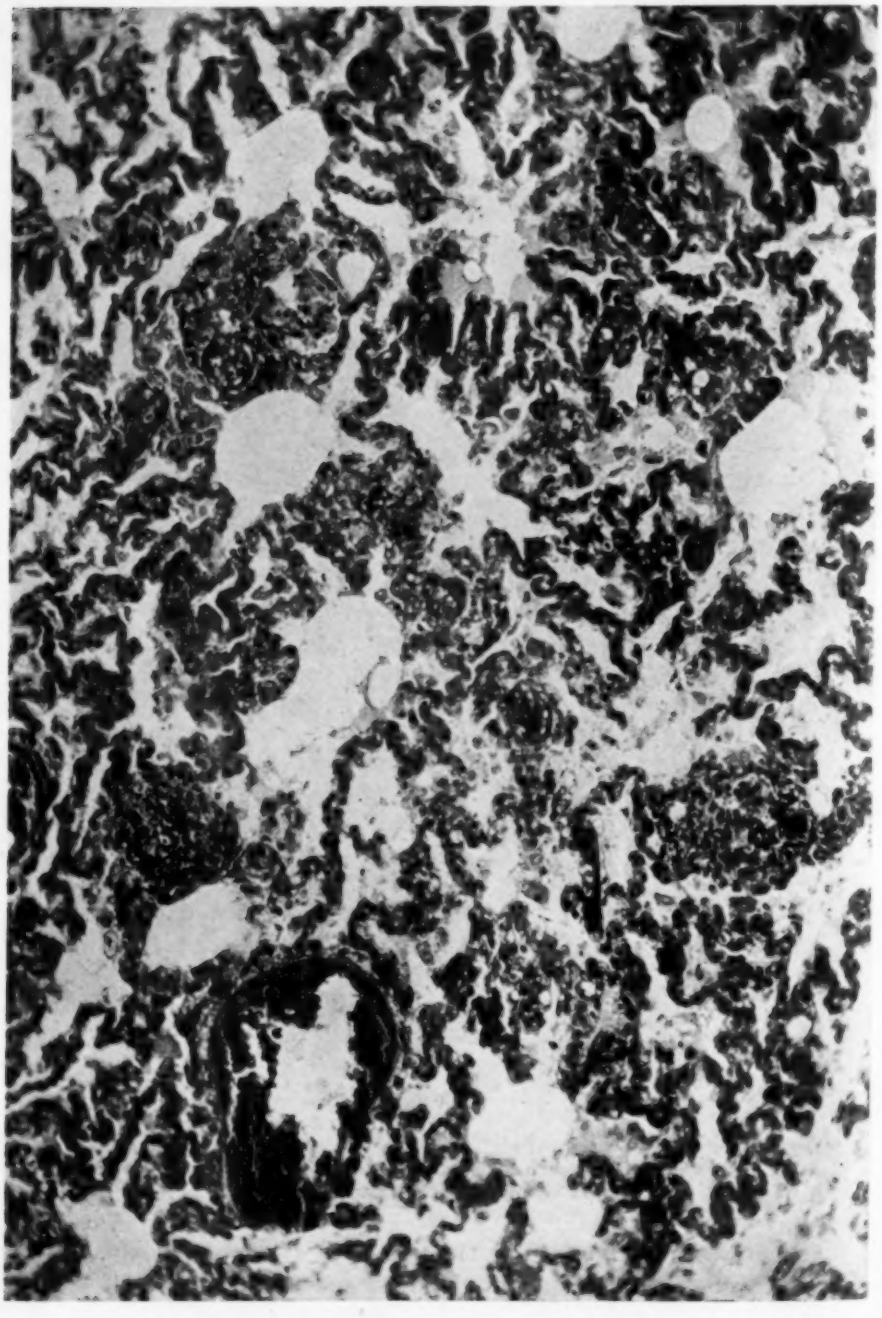

FIG. 7. Section from the lung of a rabbit which died 30 hours after receiving a lethal intraperitoneal dose of kerosene. Note capillary venous engorgement and exudate of some serum and fibrin in the alveolar spaces, as well as occurrence of thrombophlebitis.

with perivascular collections of fluid occasionally containing exudative cells (figure 11). The septa showed evidence of cloudy swelling and were infiltrated with varying numbers of polymorphonuclear leukocytes and fewer monocytes (figure 8). Alveolar edema was not seen earlier than 12 hours after treatment, but from this time on was an important part of the pathologic picture (figure 9). Frank pneumonic exudate was not discovered in any of the sections, although the leukocytic infiltrations were quite extensive in the sections from animals that survived for 12 hours or longer.

The trachea and bronchi of all animals were characteristically altered. The mucosa displayed cloudy swelling and contained numerous goblet cells. Acute congestion was striking in the submucosal tissue especially in the trachea, and the collagenous tissue was swollen and frayed. Varying numbers of monocytes, plasma cells, and lymphocytes were found in collections beneath the mucosa and in the perivascular spaces (figure 10). In the later stages coagulation necrosis and desquamation of the mucosa were frequently seen together with more extensive cellular exudate.

The picture of tracheal and bronchial damage in these animals bore a striking resemblance to that observed in rabbits following inhalation of phosgene and hydrogen chloride.[12] There was also observed the characteristic patchwork distribution of emphysema and atelectasis so frequently seen following pulmonary irritation from inhalation of noxious gases.

Diagnosis. Since acute poisoning usually follows the accidental ingestion of kerosene by small children or infants, the container is commonly either in the hands of the victim or lying near by and the sudden attack of coughing or choking directs attention to its content. If the child is unconscious, the odor of kerosene is readily recognized on the breath, vomitus or stomach washings.

Clinical laboratory procedures offer little significant information.[4, 6, 9, 11] If additional confirmation of the presence of shock or impending shock is needed, it may be obtained by a study of the blood picture which ordinarily reveals an elevated white blood count with increase in the percentage of polymorphonuclear leukocytes, and evidence of varying degrees of hemoconcentration as revealed by determinations of the red blood count, hemoglobin, hematocrit and whole blood or plasma protein levels. The urine may contain albumin, casts and red cells and may retain the odor of kerosene for some days. This characteristic odor is also present in the feces.

Prognosis. In fatal cases of kerosene poisoning death usually occurs in from two to 20 hours, but may be delayed in rare instances as long as 48 hours. The percentage of fatalities varies in several series of reported cases. Waring [4] reported two deaths in 23 cases; Nunn and Martin [6] six in 65 cases, and Farabaugh [5] five in 120 cases. These figures result in an average fatality of 6.7 per cent.

If gastric lavage is instituted promptly and continued persistently at frequent intervals, most patients will recover rapidly without serious sequelae.

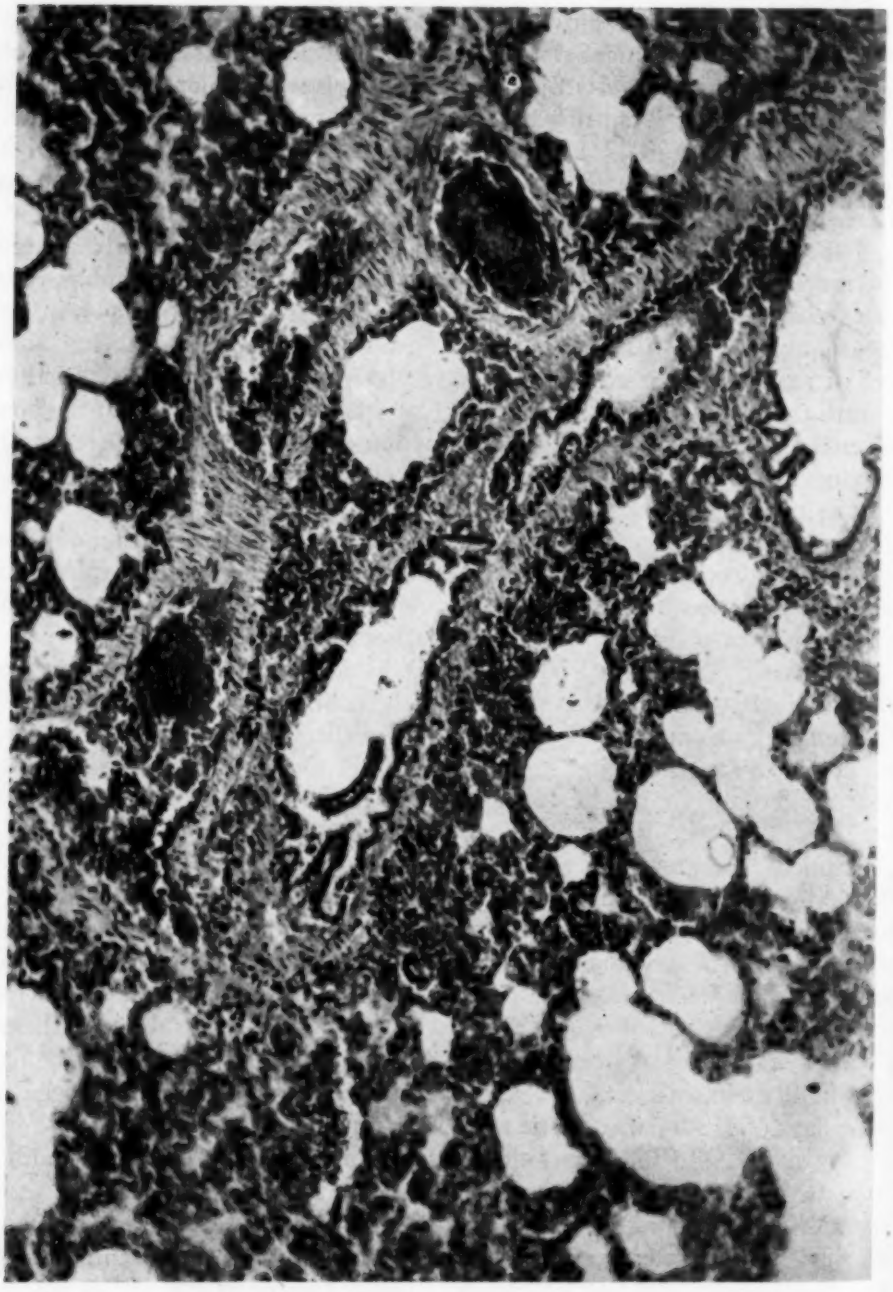

FIG. 8. Section from the lung of a rabbit which died 24 hours after receiving an intraperitoneal injection of kerosene. Note capillary venous engorgement and cellular exudate in septa and peribronchial tissue.

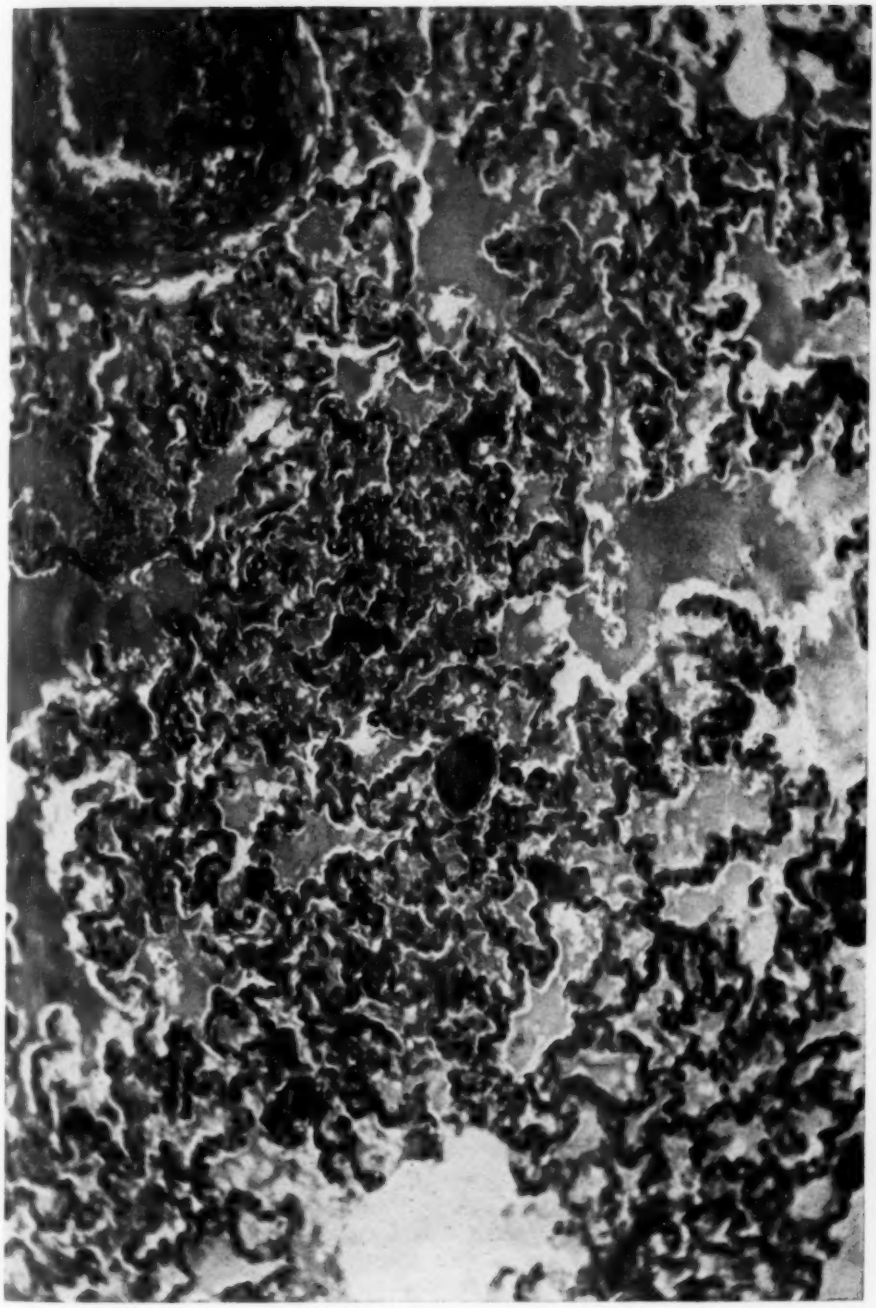

FIG. 9. Section from the lung of a rabbit which died 24 hours after an intraperitoneal injection of kerosene. Note intense alveolar edema and vascular engorgement.

FIG. 10. Section from the trachea of a rabbit receiving a lethal dose of kerosene by intraperitoneal injection with death occurring 11 hours later. Note extreme vascular engorgement and edema of tunica propria with scattered inflammatory cellular infiltration.

FIG. 11. Section from the lung of a rabbit which died 24 hours after an intraperitoneal injection of kerosene. Note capillary congestion, intense edema, and evidence of vascular and bronchial injury.

If treatment should be delayed or if poisoning is severe, pulmonary irritation offers the greatest hazard. This may be characterized by mild bronchial catarrh or severe acute pulmonary congestion and edema followed by interstitial or alveolar pneumonia. Prognosis is always grave when these severe complications are present. This is due both to the depleting effects of the systemic intoxication induced by kerosene absorption, and to the underlying lung damage and its continuing extention resulting from the presence of kerosene in the lung parenchyma.

Skin lesions caused by local application of kerosene vary in degree from a mild dermatitis to severe third degree burns, the prognosis of which depends on the extent of the skin surface involved.

Lesions produced by intra- or subcutaneous injection of kerosene required several months for healing (Waldstein).

Therapy. Among the chief therapeutic objectives should be the dilution of kerosene in the body and its removal as quickly as possible. Both of these conditions are accomplished by immediate and continued gastric lavage using large quantities of warm water or dilute baking-soda solution, and continuing lavage until the odor of kerosene is no longer detected in the washings. These measures also aid in preventing vomiting or regurgitation with aspiration of kerosene. Since the severity of the poisoning depends largely on absorption from the gastroenteric tract, it may be desirable also to give saline cathartics, and high colonic enemas or colon irrigations.

Other therapeutic measures should be supportive and designed to prevent shock, maintain the circulation and respiration, minimize pulmonary edema, and prevent if possible the development of pneumonia. In accordance with the clinical indications, the use of hypertonic glucose solution by intravenous injection may be of value to the heart muscle and liver and may aid as well in the prevention of pulmonary edema. With respect to pulmonary edema, hypodermic medication with atropine and ergotamine may be helpful, and coramine or metrazol helps in maintaining effective cardiorespiratory function. Symptoms and signs of acute anoxia should be immediately combated by the efficient administration of oxygen.

In an attempt to prevent that most serious complication, pneumonia, there can be no serious objection to the use of relatively small doses of one of the sulfa drugs, preferably sulfathiazole, sulfadiazine or sulfamerazine. Ten grains twice daily for adults, with the dosage for children in proportion, should be adequate for this purpose. If pneumonia should develop, the dosage may be adjusted accordingly. In gravely ill patients whole blood and plasma transfusions are of great value.

Since liver damage is not insignificant in kerosene poisoning, measures designed to prevent or minimize this complication should be undertaken. If conditions permit, a diet should be prescribed containing generous amounts of carbohydrate and protein and very little fat, supplemented by cod liver oil

concentrate, ascorbic acid, liver extract, thiamin and Brewer's yeast tablets, as advocated by recent investigators of liver dysfunction.

Summary

A typical case of fatal kerosene poisoning in a child is reported in considerable detail, together with the gross and microscopic postmortem findings, and the clinical aspects of this type of intoxication are presented extensively.

The lethal oral dose (LD_{50}) of a series of different commercial brands of kerosene was found to be approximately 28 ml. per kilogram of body weight for adult rabbits, and 20 ml. per kilogram for adult guinea pigs. By intravenous injection the lethal dose for rabbits was about 0.18 ml. per kilogram and 6.6 ml. per kilogram when administered intraperitoneally. Young rats were found to be more susceptible to the poisonous effects of kerosene than adult animals.

Evidence is presented to support the thesis that in kerosene intoxication pulmonary injury may be sustained from the kerosene carried to the lung by way of the blood stream, as well as from the direct introduction of the fluid into the lungs by aspiration, and that this former route is of great importance in the development of the lung damage which results primarily from vascular injury. Because of the fact that absorption with consequent deleterious systemic effects continues so long as kerosene remains in the gastroenteric tract, every effort should be made to remove it as quickly as possible in treating cases of kerosene poisoning.

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SYNDROME OF AURICULOVENTRICULAR ACCESSORY PATHWAY *

By GEORGE KAPLAN, Major, M.C., A.U.S., and THEODORE D. COHN, Captain, M.C., A.U.S., *Pittsburgh, California*

THE first record of this abnormality was described by Wilson [1] in 1915, who believed it to be vagal effect. Wedd [2] reported another such case in 1921 and called it "A–V nodal rhythm." Hamburger [3] in 1924 reported four cases of "intraventricular conduction disturbances with unusual clinical features."

Wolff, Parkinson and White [4] were the first to recognize this abnormality as a clinical syndrome. The possibility of an accessory pathway producing this picture was first suggested by Holzmann and Scherf.[5]

Electrocardiographic tracings have the following characteristic pattern:

a. Short PR interval.
b. Prolonged QRS complex with slurring.
c. Usually oppositely directed T waves.

In a series of 1,672 consecutive electrocardiograms taken at this hospital, this syndrome was observed twice.

CASE REPORTS

Case 1. A white soldier, age 21, with three years and eight months service in the Army, was admitted to the hospital with a history of periodic paroxysms of palpitation of three years' duration. These attacks had a sudden onset at irregular intervals of one to six months and a sudden offset. They were associated with weakness, profuse perspiration, nervousness and pounding in the chest. Between attacks he was able to indulge in excessive physical activity such as football, swimming, and boxing without difficulty. The paroxysms came on at any time and without any relationship to exercise. There was no previous history of rheumatic fever, chorea, or tonsillitis. He had no dyspnea on exertion, except during his attacks of paroxysmal tachycardia. No member of his family had any symptoms which would lead one to suspect the presence of a similar condition.

Physical Examination. The patient was a well-developed, male adult, 5 feet 7¾ in. tall, weighing 142 pounds, whose blood pressure was 138 mm. Hg systolic and 80 mm. diastolic. Heart: Point of maximum impulse was in the fifth interspace within the midclavicular line. The sounds were of good quality and there were no murmurs. The rhythm was regular sinus and the heart rate 84 per minute. There was a normal cardiac response to exercise, the aortic second sound was greater than the pulmonic second sound. The remainder of the physical examination was normal.

Laboratory Data. Urine showed a specific gravity of 1.022, no albumin, no sugar; microscopic examination negative. Blood Count: Hemoglobin 100 per cent, white blood count 7,400, polymorphonuclear neutrophiles 74 per cent, lymphocytes 20

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From The Medical Service, Station Hospital, Camp Stoneman, California.

per cent, monocytes 4 per cent, eosinophiles 2 per cent, blood cholesterol was 158 mg. per 100 c.c. of blood; basal metabolic rate minus 5 per cent; sedimentation rate 4 mm. per 60 minutes by the Cutler method; Kahn reaction was negative.

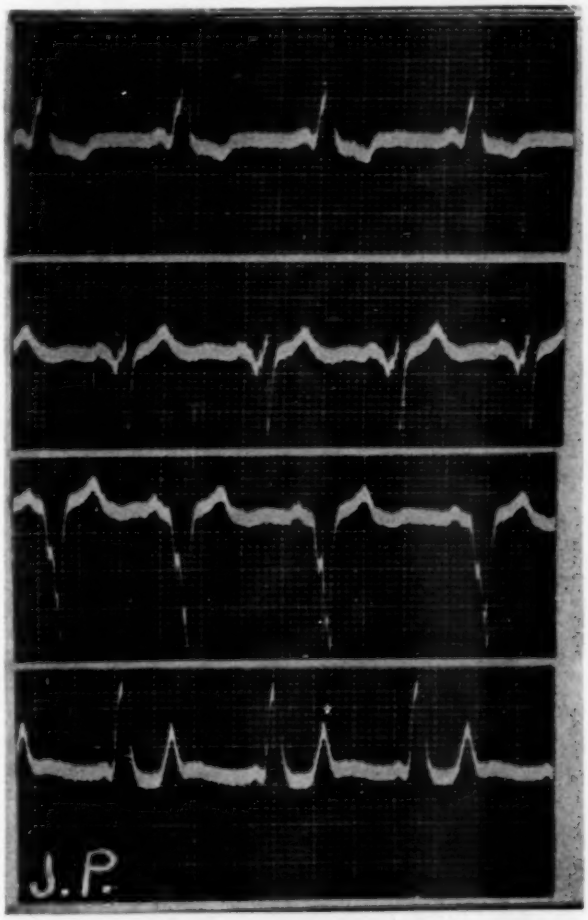

FIG. 1. J. P.

Rate: Auricular 85; ventricular 85.
PR Interval—0.10 Sec.
QRS Complex—0.12 Sec.
Rhythm: Regular Sinus.
P Waves—Upright in I, II and III.
QRS Complexes—Upright, notched and slurred in I; inverted and slurred in II; deeply inverted, slurred and notched in III.
T Waves—Inverted in I; upright in II and III.
Lead IV—Initial Deflection positive. QRS 0.12 sec. T waves upright.

The telecardiogram showed the cardiac silhouette to be well within the limits of normal. The electrocardiogram (figure 1) showed a short PR interval with a long QRS complex and oppositely directed T waves. This patient had practically no disability because of his great capacity for physical work without precipitating an attack.

Case 2. A white soldier, age 28, was admitted to the hospital in an acute attack of paroxysmal auricular tachycardia. The patient was dyspneic, apprehensive, with a cold clammy perspiration and an ashen gray pallor to the skin. His heart rate was 210 per minute and the sounds were booming in character. Ocular pressure

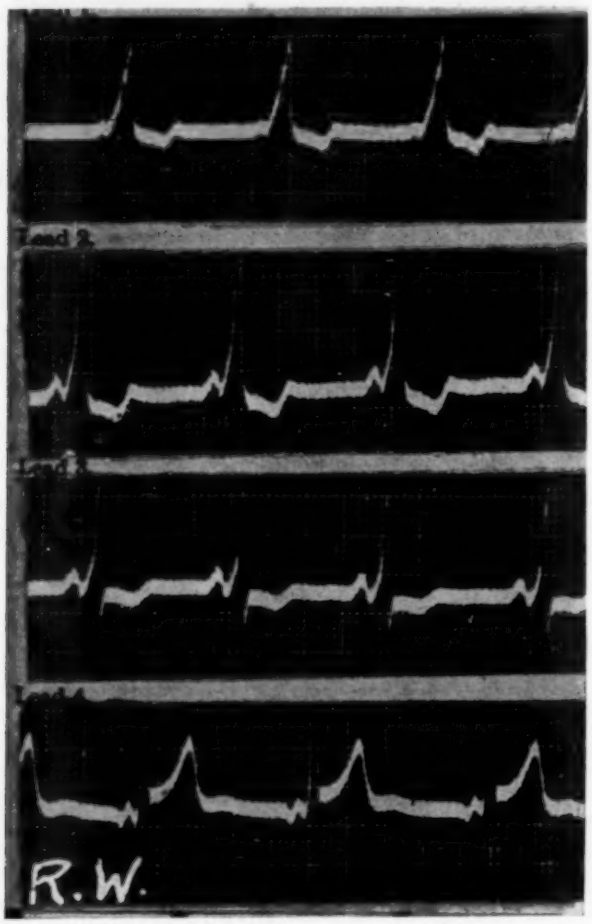

FIG. 2. R. W.

Rate: Auricular 75; ventricular 75.
PR Interval—0.10 Sec.
QRS Complex—0.14 Sec.
Rhythm: Regular Sinus.
P Waves—Upright in I, II and III.
QRS Complex—Upright, notched and slurred in all leads.
T waves—Inverted in I, II and III.
Lead IV—P waves diphasic. Initial deflection positive. QRS 0.14 sec. T waves upright.

caused an immediate cessation of the attack. The patient gave a history of very frequent attacks of "palpitation" for the past five years. These paroxysms were brought on by slight exertion such as a short hike and lasted 30 minutes to 24 hours. An attack could be produced at will. Ocular pressure would invariably stop the attacks. Between the attacks he was free of symptoms and felt well.

Previous history did not reveal rheumatic fever, chorea, or tonsillitis. No member of his family had any symptoms which would lead one to suspect the presence of a similar condition.

Physical Examination. The patient was an adult, white male, 5 feet 9 in. tall and weighing 150 pounds. Heart: Point of maximum impulse was in the fifth interspace within the midclavicular line. The rhythm was regular sinus, and the rate 74 per minute. There were no murmurs, and there was a normal cardiac response to exercise. The aortic second sound was greater than the pulmonic second sound. Fluoroscopic examination of the heart in all positions revealed a normal cardiac silhouette and no enlargement of any chamber. The remainder of the physical examination was normal.

Laboratory Data. Urine and blood counts were normal; Kahn reaction was negative. Basal metabolic rate minus 14 per cent. The electrocardiogram (figure 2) showed a short PR interval with a long QRS complex and oppositely directed T waves. This patient was definitely disabled because of the ease with which an attack developed.

Discussion

Aberrant conducting tissue bridging the right auricle and ventricle and known as the right lateral bundle was described by Kent.[6] The most reasonable explanation of this syndrome was advanced by Wolferth and Wood.[7, 8] According to their concept, the impulse originates in the normal pacemaker

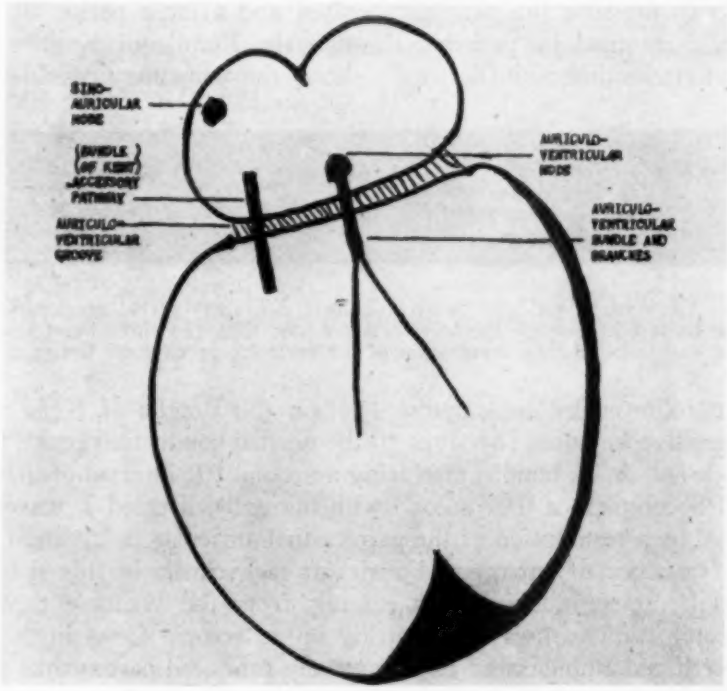

Fig. 3. Schematic drawing showing relation of accessory pathway to the normal conduction system.

(sino-auricular node). It traverses the short distance to the accessory pathway (figure 3), thus causing the short PR interval. By arriving prematurely in the musculature of one ventricle it produces the pattern of a bundle branch block. This explanation is enhanced by the experimental work of Butterworth and Poindexter,[9] who by short-circuiting the impulse in animals, produced a typical electrocardiographic tracing of this syndrome. Wood, Wolferth and Geckeler[10] demonstrated histologically an accessory Bundle of Kent in a case of "Short PR Interval and Long QRS Complex."

The electrocardiogram of the patient in case 2, taken during one of his attacks (figure 4), shows paroxysmal auricular tachycardia with a normal

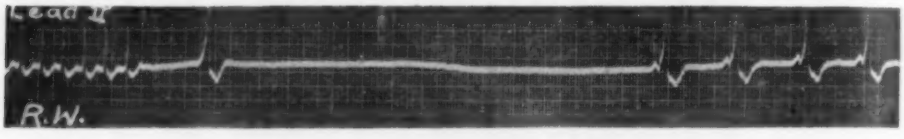

FIG. 4. Auricular paroxysmal tachycardia rate 210, followed by a long period of asystole and return of normal sinus rhythm via the accessory pathway.

QRS interval of 0.06 second. This is in accord with the concept advanced that the Bundle of Kent is unable to carry the rapid succession of impulses and thus these impulses now traverse the normal cardiac pathways. With eyeball pressure the paroxysm ceased and after a period of asystole the impulse resumed its pathway through the Bundle of Kent. Another strip of electrocardiogram (figure 5) shows the temporary cessation of the

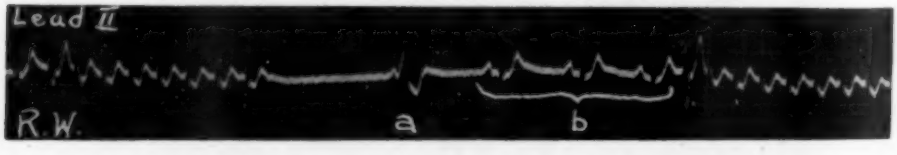

FIG. 5. Paroxysmal auricular tachycardia rate 200, short period of asystole followed by (*a*) one heart beat through the accessory pathway, then (*b*) three heart beats via the normal pathway followed by a resumption of the auricular paroxysmal tachycardia.

paroxysm followed by one impulse (*a*) via the Bundle of Kent and then three successive impulses (*b*) through the normal conduction pathway of the A. V. node and A. V. bundle, producing a normal PR interval of 0.16 second and a QRS complex of 0.07 second with normally directed T waves. This is followed by a resumption of the paroxysmal auricular tachycardia.

The frequency of paroxysmal auricular tachycardia in this syndrome is explained by retrograde impulses passing from the ventricle through the normal conduction pathway and setting up an ectopic focus in the auricle. Butterworth and Poindexter[9] experimentally produced paroxysmal auricular tachycardia in the cat's heart by retrograde impulses. This concept is also advanced by Wolferth and Wood.[8]

Summary

1. Two cases of "syndrome of auriculoventricular accessory pathway," occurring in young adults with no clinical cardiac disease, are described.

2. Short PR interval and long QRS complex are the characteristic electrocardiographic findings.

3. The mechanism of this anomaly is discussed.

4. The clinical syndrome is characterized by repeated attacks of paroxysmal auricular tachycardia.

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THE SYNDROME OF PAROXYSMAL TACHYCARDIA WITH SHORT P–R INTERVAL AND PROLONGED QRS COMPLEX, WITH REPORT OF TWO CASES*

By JULIUS R. PEARSON, Captain, M.C., A.U.S., F.A.C.P., and ALBERT W. WALLACE, Lt. Colonel, M.C., A.U.S., F.A.C.P.

THAT type of paroxysmal tachycardia associated with a short P–R interval and prolonged QRS complex has long provoked the empirical query of the anatomist, physiologist and clinician alike. The comparative paucity of cases and the diversity of conclusions have made for difficulty in final interpretation of this unusual entity. Since Wilson's [1] original description in 1915, much has been added to crystallize it, and each new work presented has stimulated further investigation in an effort to arrive at complete clarification.

In 1893, Kent,[2a, b] working with mammalian hearts, paved the way for the most acceptable theory on the mechanics of this anomaly, by exposing accessory auriculoventricular conduction bundles. In 1913 and 1914, he [2c, d, e, f, g] demonstrated that muscular bridges, connecting the auricles and ventricles, occasionally were to be found in the human heart, which could transmit an impulse independently of the bundle of His. Glomset and Glomset,[3] in their study of mammalian and human hearts, have substantiated the existence of myoneural bridges scattered abundantly over the atria and between the auricles and ventricles in the auriculoventricular groove. Very recently, Wood, Wolferth and Geckeler [4] have examined the heart of an individual who, in life, demonstrated the syndrome of "paroxysmal tachycardia with short P–R interval and prolonged QRS complex," and who died in the last one of these attacks. The heart presented no gross abnormality or evidence of disease, but serial microscopic sections of the auriculoventricular groove in the position at the right lateral border of the heart, as originally demonstrated by Kent, showed muscular bridges connecting the auricle and ventricle. Still further credence to the tenet that these myoneural connections form the pathway for aberrant conduction to produce the abnormal electrocardiograms is supplied in the recent experimental work of Butterworth and Poindexter,[5, 6] who short-circuited the normal auricular conduction system by leading off electrical impulses from the auricle, amplifying them, and using them to stimulate the ventricle. They reported that "the auricular contractions remained perfectly constant, but by turning the amplifier on and off, the abnormal complexes of the short P–R—wide QRS type could be produced at will."

Before any physiological explanation for the syndrome can be studied,

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and because it has been attributed by some to extracardiac factors, it is well to mention briefly some of the responses of the heart to stimulation by its afferent nerves or by various affecting drugs. The cardio-inhibitory vagus nerve is the heart's principal brake; the right vagus mainly subjects the sino-auricular node; the left similarly, but to a lesser degree, controls the auriculo-ventricular node. Each node also receives a partial nerve supply from the opposite side. Right vagal excitation leads to slowing or complete cessation of the auricular beat, with subsequent slowing of the ventricular beat. Stimulation of the left vagus leads to ventricular retardation by depressing auriculoventricular conduction and interfering with the auricular impulses. Both nerves constantly exhibit a certain amount of reflex tone which depends on "afferent impulses flowing to the vagus center along the sinus and aortic nerves." [7] Large doses of atropine frequently paralyze the vagus and eliminate its tonic effect, with resulting escape of the heart at greater speed. The carotid sinus is an important secondary regulator of the heart rate, and pressure upon it produces a stimulating vagal effect and decreases the heart rate. Acetyl-beta-methylcholine chloride causes only slight depression of the sino-auricular node, but acts mainly to depress auricular muscle, the auriculoventricular node and the bundle of His.[8] The supraventricular action of digitalis usually stimulates the vagus and increases the excitability of the carotid sinus. These actions can be negated by atropine. Also, digitalis has a direct action on the conduction bundle, depressing conduction therein, and this action cannot be annulled by atropine. Quinidine is a general protoplasmic poison which prolongs the refractory period of the sino-auricular node and depresses conduction in the auriculoventricular node likewise, thus depressing the speed of the impulse formation and conduction. This slowing is not under vagal influence because it occurs after the administration of atropine, and this drug has no ability to alter the auriculoventricular block caused by the quinidine. All of these observations were pertinent in our experiments to be described below.

The anomalous conduction involves consideration of both extra and intracardiac mechanisms. The most comprehensible, though not unanimously accepted, theory is the one presented by Wolferth and Wood [9] and by Holzmann and Scherf.[10] These workers propounded a short-circuiting of the auriculoventricular node via accessory auriculoventricular bundles to explain the lessened auriculoventricular conduction time. The asynchronous beat of the ventricles and prolonged QRS complex they attributed to the stimulation of first one ventricle, and then to the other via septal-muscular conduction, rather than to the simultaneous conduction through the bundle of His and its ramifications. As to the clinical expression of paroxysmal tachycardia, they assumed a retrograde conduction over the accessory auriculoventricular path, causing a reëntry phenomenon in the auricles, and producing to all intents and purposes a circus-like movement at a rapid rate. This prophecy is brought a step closer to acceptability by the discovery of Wood

et al.,[4] in 1943, of such anatomic muscular bridges at the right lateral border of the heart in an individual who, in life, presented the syndrome, thus supplying the keystone to the bridge between the clinical and anatomico-physiological aspects of the problem.

Other theories are worthy of review, though none has stood the test of time nor has had as many adherents as have the champions of the accessory pathway. Wilson[1] concluded that the "vagi were partially responsible for both the change in location of the pacemaker and the abnormality of the ventricular complex." Wolff, Parkinson and White,[11] who clearly established the syndrome, and for whom it was named, first assumed a functional bundle branch block. White has forsaken this assumption for the accessory pathway theory. Parkinson, with Hunter and Papp,[12] later believed that the anomalous beat arose near, but not within, the sinoauricular node, and that the normal ventricular complex was interfered with by a ventricular extrasystole which arose prematurely and low in one bundle branch. Holzmann and Scherf[10] suggested, and Cossio, Berconsky and Kreutzer[13] further hypothesized that the abnormal conduction was the result of excitation of a hyperirritable ventricular focus by the auricular systole. Tung[14] stated that "vagal influence or aberrant distribution of the vagi may be responsible for (the functional) ventricular block in healthy subjects. Release of vagal tone may produce a reversion of the abnormal to the normal mechanism." Recently, Scherf[15] mentioned another possibility in the assumption of a "functional longitudinal dissociation of the auriculoventricular system of the mammalian heart." Katz[16] suggests several possibilities, viz., first that the conduction represents "nodal rhythm or tachycardia with aberrant conduction," the cause "probably similar to that seen in premature auricular systoles except that the aberrant by-pass remains fixed as long as the impulse arises in the A–V node"; second that "a region of block develops in the interventricular septum so that the electrical effect of stimulation of the septum, normally recorded as an isoelectric period, becomes apparent" with the presupposition of "a region with a refractory period longer than normal located near the base of the septum, which alters the electrical resultant; third that "there is a direct path between the sinus node and the ventricle, which permits the impulse in part to pass quickly by the A–V node," "the impulse so conducted shares the control of the ventricles with the impulse transmitted in the usual way." It is apparent in the study of the work of all these men, that there is an element of acceptability in each of their varying theories. To the present, each successive worker on this problem has presented electrocardiographic data to illustrate his interpretations.

In spite of the fact that there is a difference of opinion on the physiological basis for the syndrome, all do agree on its clinical aspects. It may occur at any time from infancy to old age, in either sex, but to date, most of the reports have been in males, and may be associated with an otherwise normal heart or a concomitant cardiovascular or renal lesion. The paroxysm may

come on while the patient is at rest, or after strenuous exercise, or emotion, or may even be an expression of allergy.[17] The palpitation may not make itself evident, the syndrome may be found accidentally by electrocardiogram, or it may be the presenting feature. Usually the tachycardia is of the simple auricular type, but, rarely, it is on a basis of paroxysmal auricular fibrillation or flutter, or paroxysmal ventricular tachycardia.[18, 19] The history is commonly that of many years' duration with remissions. The diagnosis is apparent at a glance at the electrocardiogram when the features of the abnormal conduction are present, namely, a short P–R interval with a prolonged QRS complex which resembles bundle branch block of left, right or intermediate type. In some of the cases, vagal influence is capable of altering this electrocardiogram; in others, no effect is noted. The anomalous conduction may persist independently or in spite of all efforts to convert it to normal, or it may vary unpredictably as a result of spontaneous correction, vagal stimulation or medication with digitalis or quinidine. Previous to the case reported in 1943 by Wood et al.,[4] it was believed that, of itself, the syndrome was probably a benign one, incapable of producing myocardial damage if the bout of tachycardia did not persist too long, and better left without medication, provided the patient was acquainted with all the facts.

Among inductees in the United States Army, tachycardia, and its usual clinical counterpart, palpitation, are frequently presented for study. Two cases of this rare syndrome of paroxysmal tachycardia with short P–R interval and prolonged QRS complex appeared in a representative group of soldiers with cardiac disturbances. In one, the aberrant conduction pattern could be converted to the normal; in the other, the change was never seen spontaneously and could not be effected by any experimentation.

Case Reports

Case 1. The first patient was a young man of 30 years, who complained of bouts of palpitation occurring since childhood, after exertion, emotion, or often while at rest, and rarely, also when hungry. These bouts were usually self-limited, and he never consulted a physician about them. The present attack had started on the day previous to his coming under the observation of one of us (J. R. P.), following mild exertion and excitement, but ceased on the same night without any medication or interference. His heart rate during the paroxysm was about 260 per minute. On the next day he was asymptomatic, and his electrocardiogram showed upright P waves, P–R 0.08 second, slurring of the ascending limb and notching of the QRS in all limb leads, depressed ST segments, and inverted T waves (figure 1).

Beginning with standard tracings similar to these, the subsequent experiments recorded and discussed here were carried out.

Exercise caused mild increase in rate, but produced no change in the shape or time-relationships of the individual waves. This agrees with the findings of Roberts and Abramson [20] and with those of Fox, Travell and Malofsky,[21] but varies with those of Wolff, Parkinson and White,[11] who were able to abolish abnormal complexes by exercise and cause reversion to normal conduction, and with those of Bishop,[22] who was able to cause fleeting changes resembling the normal after exercise.

Tracings were then made with the body in various positions and under the in-

fluence of high and of low oxygen tensions, all without resulting alteration in the contour of the waves or the conduction pattern.

Indirect vagal stimulation by carotid pressure did not change the electrocardiogram with the exception of a mild slowing of the rate. This was more noticeable by pressure on the right than on the left carotid, and this finding is comprehensible since the right vagus controls the sinoauricular node. As has been pointed out, the left vagus controls the auriculoventricular node, which is not traversed by the anomalous impulse. (Carotid pressure likewise had little effect on the normal conduction pattern later obtained by quinidinization.) The inability to convert the abnormal

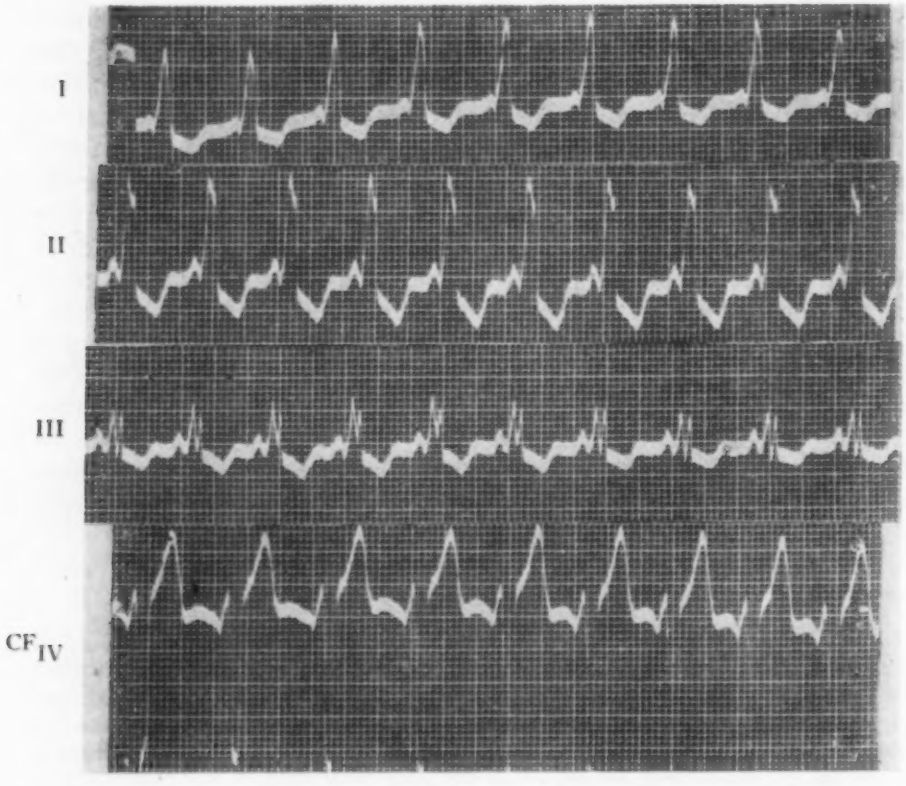

FIG. 1. 4/7/43. Tracings made on the day after the bout of paroxysmal tachycardia. No medication had been given.

graph to the normal by vagal stimulation thus differs from the findings of Wedd [23] and of Sigler,[24] and corroborates those of Roberts and Abramson and more recently of Fox et al.

Vagal paralysis by atropine had no effect on the curves and merely caused an increase in the heart's speed. This agrees with the reports of Roberts and Abramson, Bishop, and Butterworth and Poindexter, but differs from that of Fox et al., who produced shortening of the QRS complex with the increased speed, and from that of Wilson, and Wolff et al., and Tung. Wilson originally stated that the "abnormal rhythm, when spontaneously present, could be converted into the normal rhythm by the administration of atropine in doses sufficient to paralyze the vagi."

In the series of experiments with drugs having effect on the myocardium, the conduction system and the sympathetic-parasympathetic nervous systems, none caused any change from abnormal to normal conduction except quinidine sulfate. Prostigmine had no effect after atropine. Adrenalin, theophylline, ergot and morphine each

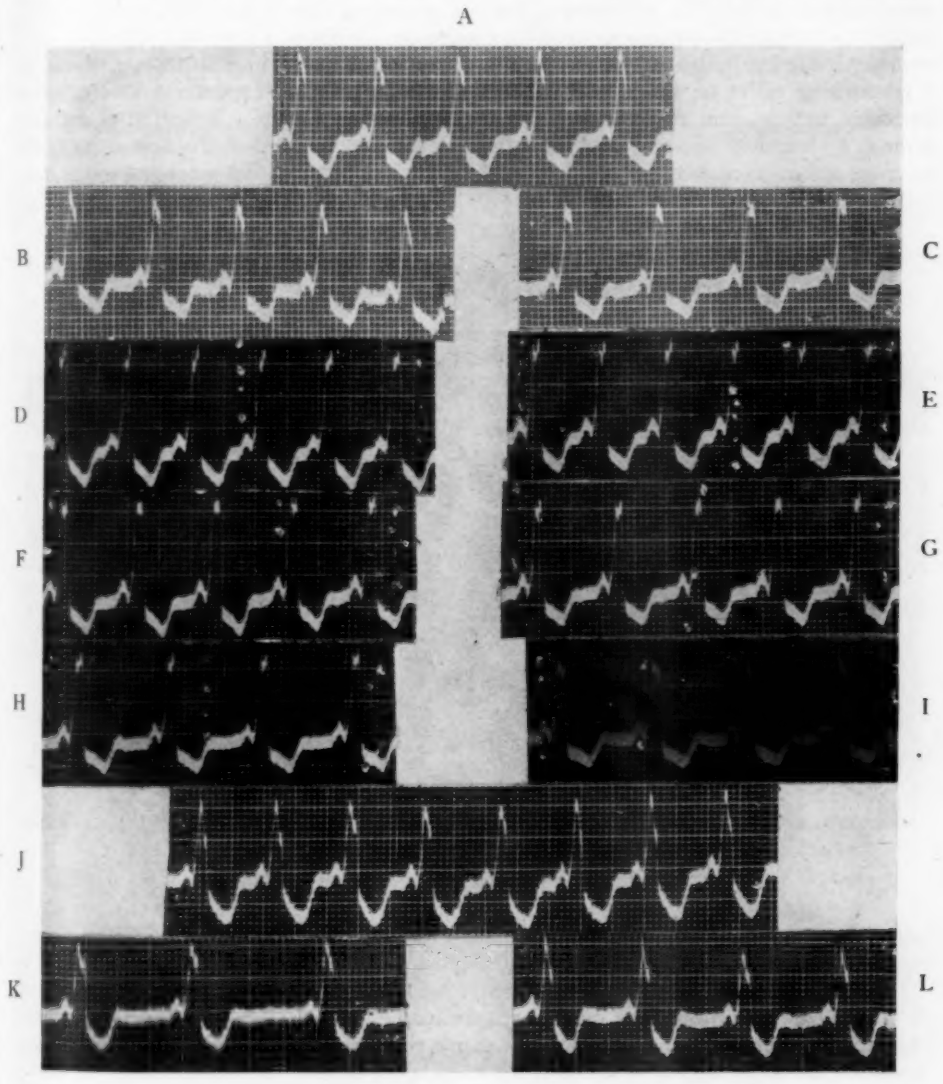

FIG. 2. (*A*) After exercise. (*B*) Left carotid pressure. (*C*) Right carotid pressure. (*D*) After atropine. (*E*) After prostigmine. (*F*) After theophylline. (G) After adrenalin. (*H*) After ergot. (*I*) After morphine. (*J*) After amylnitrite. (*K*) High oxygen tension. (*L*) Low oxygen tension. (All tracings are made in Lead II.)

slowed the heart rate moderately but did not alter the complexes in time-ratios or contours. Amyl nitrite caused only an increase in rate. Fox et al. have recently demonstrated a flexibility of the QRS under the influence of these drugs which was not confirmed here (figure 2, composite).

Tracings made under the influence of a full clinical dosage of digitalis (18 c.u. in six days) showed practically no change in the complexes except for marked slowing of the rate to 50 per minute, a sinus arrhythmia, somewhat lessened voltage, slight slurring of the ascending limb of R and lowering of the initiation of its descending limb in Lead II, rounding of the ST segments, and in Lead III, one complex which is reminiscent of those in Lead II (figure 3). This was a typical physiological-electrocardiographic demonstration of the action of digitalis in full dosage, showing a restraining effect on the sinoauricular node, depression of conduction through the auricular muscle, and direct action on the conduction bundle. Scherf and Schonbrunner [25] found in one case that digitalis in large doses abolished the abnormal QRS complexes for three weeks, and suggested that the accessory pathway was more susceptible to digitalis than was the bundle of His. Apparently the findings in our ex-

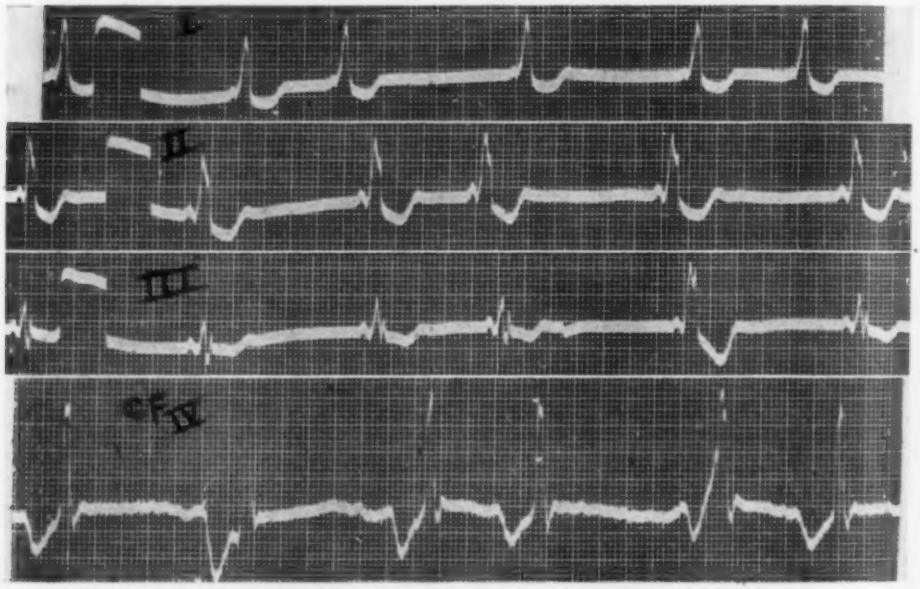

FIG. 3. After 18 cat units of digitalis had been given in a period of six days.

periment show the opposite, since the bundle of His was affected, whereas the accessory pathway was untouched.

During the entire time, physical examination revealed an inconstant impurity of the first heart sound over the mitral area, heard best during the periods of digitalization and quinidinization. The blood pressure remained fairly steadily near the level found on the days after admission to the hospital in spite of all manoeuvers. Fluoroscopically and teleoroentgenographically, the heart was well within normal limits of size and contour. There was also present a spina bifida occulta of the first sacral segment. Other than this, no abnormalities or congenital anomalies were discernible on physical or clinical examination. Circulation times, measured by the calcium gluconate method, were determined while the heart was in abnormal conduction and then in normal conduction by means of quinidine. In the former, the arm to tongue time was 15 seconds; in the latter, 11 seconds.

When the heart had reasonably emerged from the influence of digitalis (18 days after the last dose), the patient was given quinidine sulfate, after eliminating possible

sensitivity, in four repeated doses of gr.v each. One hour later his electrocardiogram showed changes to the normal type of conduction (figure 4). The tracings showed: upright P waves in limb leads; P–R 0.16 second; QRS 0.06 second; deep S in Lead I, small S in Lead II; small Q in Lead III; ST practically isoelectric; T diphasic in Lead III, otherwise upright. At this time the total length of the P–T was about 0.48 second whereas on the first day the abnormal conduction measured about 0.44 second. The normal conduction was permitted to revert to the abnormal on the same day

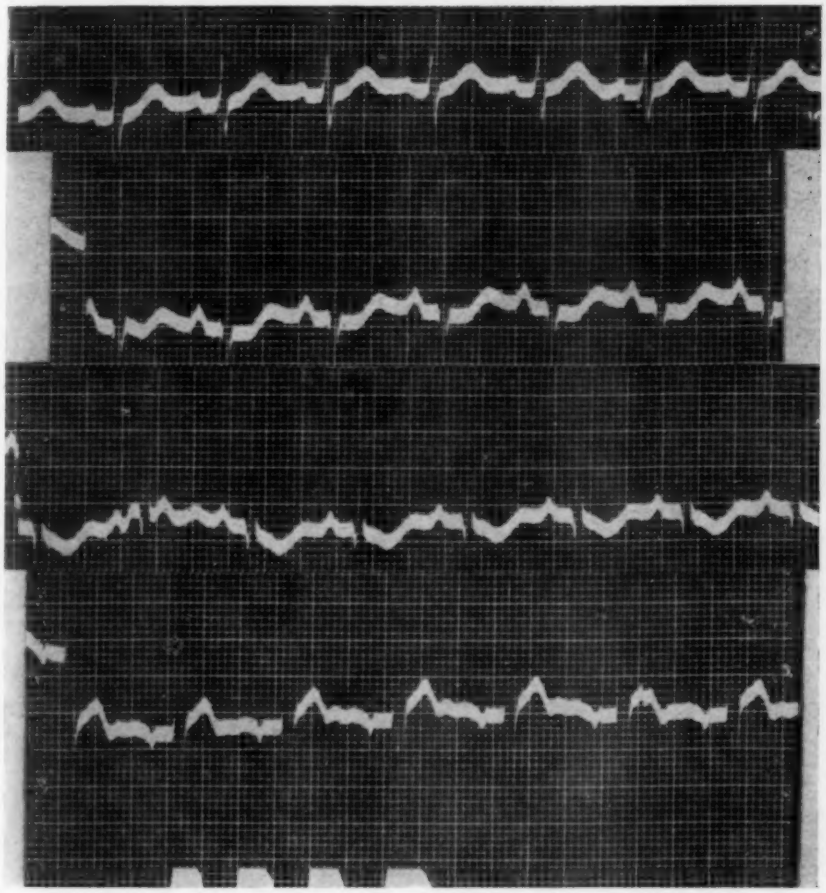

FIG. 4. After quinidine sulfate, given in gr. v doses every two hours for four doses. The tracings were made one hour after the fourth dose.

merely by discontinuing the quinidine, and at a later date reconverted to normal by repeating the experiment. Again indirect vagal stimulation by carotid pressure, and vagal atonia by atropinization were produced, but no change to the abnormal type of conduction occurred, and no alteration of this picture's time-ratios or contours was observed. The conversion of the unusual tracings to the normal type by quinidine agrees with the work of Roberts and Abramson,[20] Wolferth and Wood,[9] and Levine and Beeson.[19] The first authors reasoned that the lower level of development of the anomalous conduction tissue made it more easily responsive to depressants like

quinidine than was the bundle of His. Wolferth and Wood, however, argued that the quinidine also caused reduction of myocardial irritability in general, and that "this therapeutic result cannot be used as an argument in favor of the hypothesis of an accessory pathway of conduction." This denial cannot be accepted without reserve in the face of the failure to convert the abnormal conduction to the normal after our experiment with acetyl-beta-methylcholine chloride and atropine followed by quinidine, which will be discussed below.

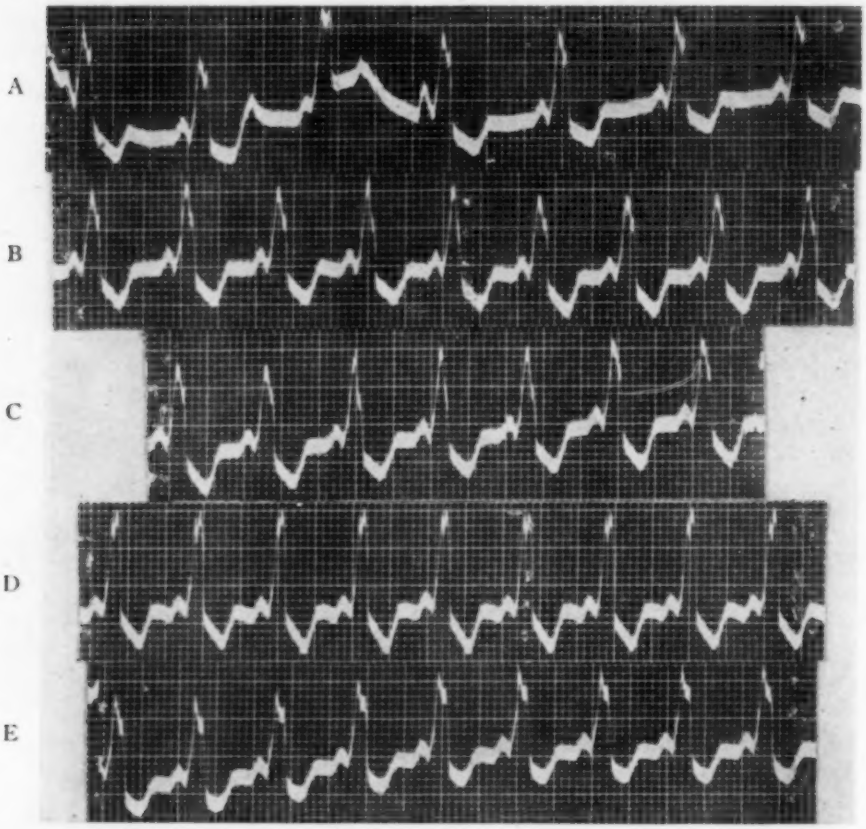

FIG. 5. Lead II in each tracing. (*A*) Standard. (*B*) 1 minute after mecholyl subcutaneously. (*C*) 5 minutes after mecholyl. (*D*) 2 minutes after atropine intravenously. (*E*) 20 minutes after atropine.

After a four day rest period to eliminate quinidine from his body, a standard set of tracings was made. The PR measured 0.08 second, the QRS, 0.12 second. His blood pressure was 110 mm. Hg systolic and 60 mm. diastolic, and his heart rate, 90 per minute. Immediately thereafter, he was given 0.2 gm. acetyl-beta-methylcholine chloride subcutaneously. There was full clinical response, but with moderate tachycardia (120 per minute) instead of the expected slowing, and but little change in blood pressure (100 mm. Hg systolic and 50 mm. diastolic). The entire picture of flushing, lacrimation, salivation, profuse perspiration and respiratory bubbling was terminated by the intravenous injection of 0.0012 gm. atropine sulfate. His blood pressure rose at once to 170 mm. Hg systolic and 100 mm. diastolic, and his heart rate

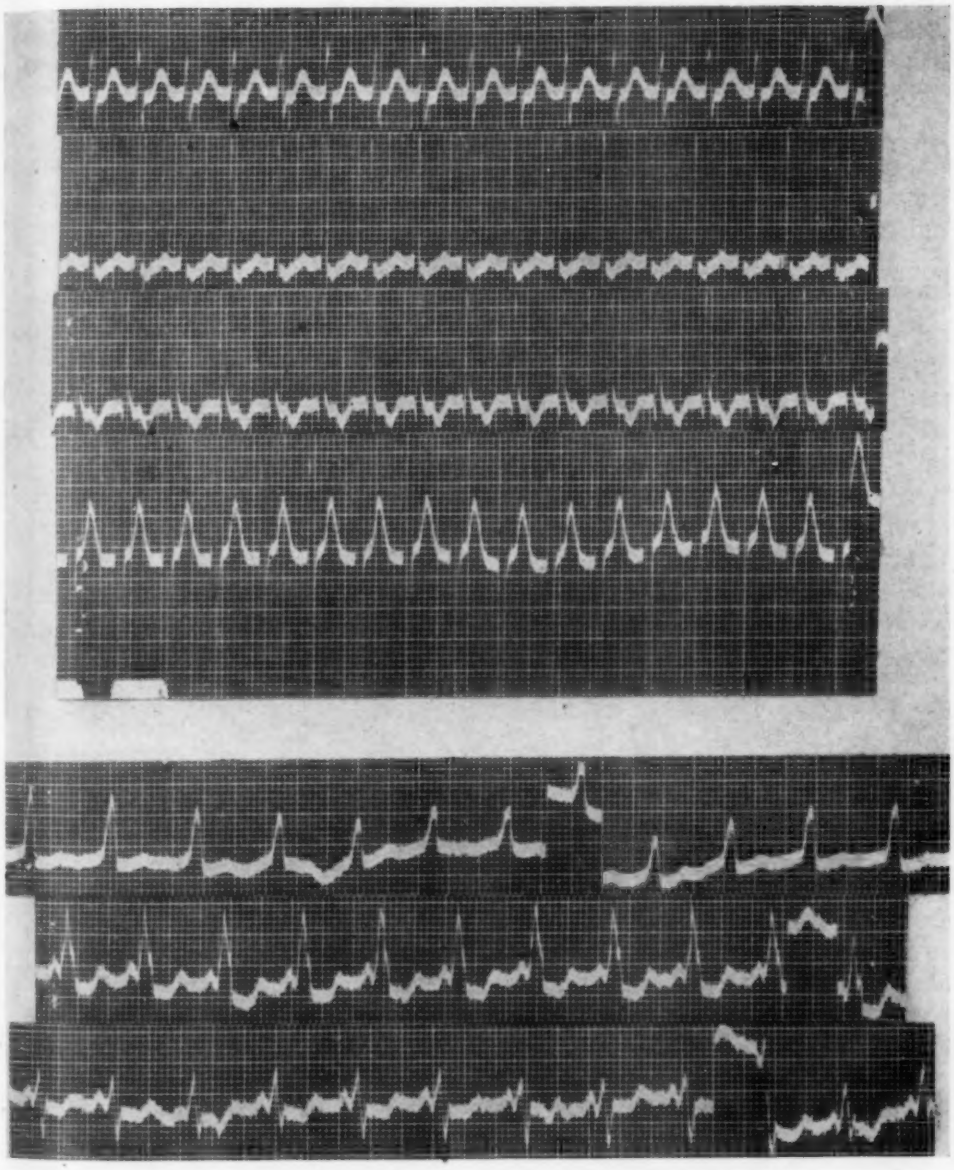

FIG. 6. During attack of paroxysmal tachycardia (above) and immediately after its conclusion (below).

to 130 per minute. The only alteration in the graphs resulting from the mecholyl was a slight depression of the descending limb of the R wave and a similar depression of the ST segment. The atropine, however, banished this effect, and 20 minutes after the atropine had been given, the tracings did not differ from the standard except for slight rounding of the ST segment. The PR measured 0.08 second and the QRS, 0.10 second; the PT was 0.04 second shorter than the original standard (figure 5).

This experiment, with exactly the same end results, was repeated one month later. The blood pressure rose from 120 mm. Hg systolic and 80 mm. diastolic to 170 mm. Hg systolic and 100 mm. diastolic, and the electrocardiographic measurements duplicated those mentioned previously.

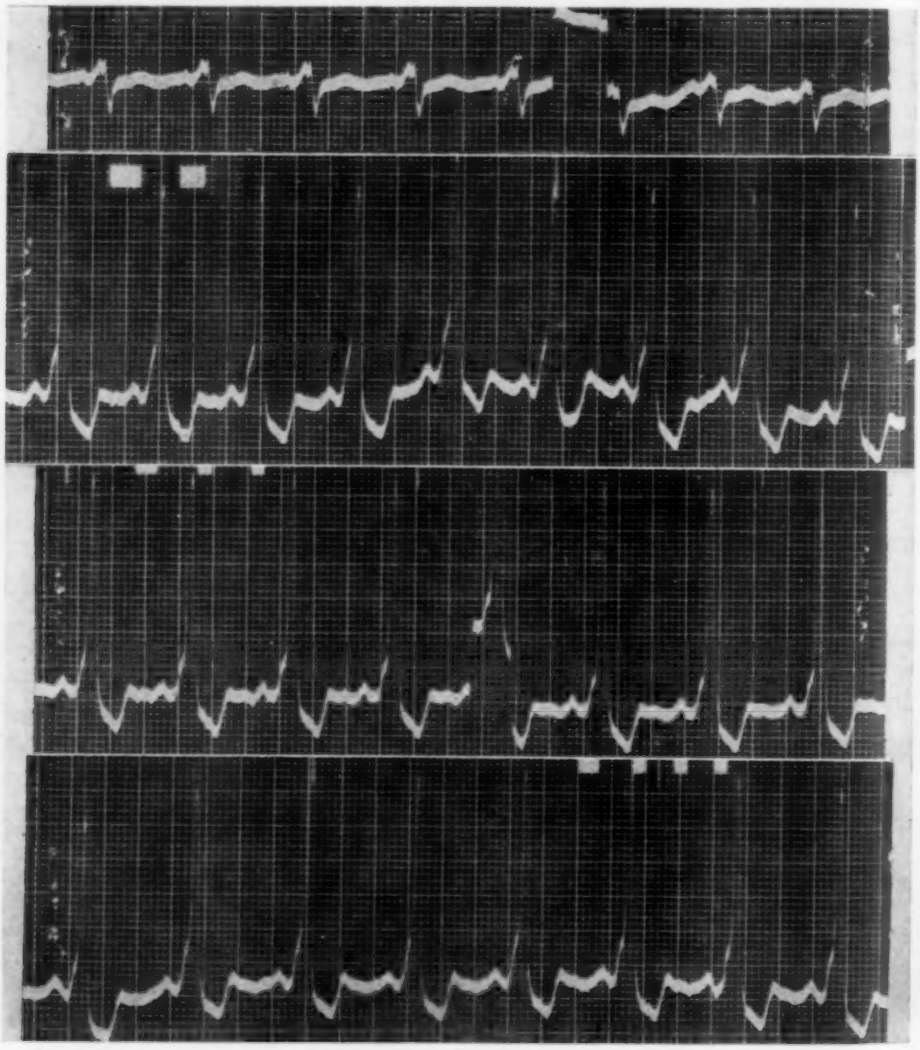

FIG. 7. Case 2. Tracings of the aberrant conduction pattern, from which there was no variation under any circumstance.

Immediately following this experiment the first time, an attempt was made to quinidinize the patient in the same simple manner as previously, with divided doses by mouth. This time no conversion to the normal type of conduction occurred, and the only change consisted of a lengthening of the PT to 0.52 second, a mild slowing of the rate, and a minute depression of the descending limb of the R wave and the ST

segment. He was again rested and reëstablished to normal conduction on the next day with the simple method of quinidinization. On subsequent days, quinidine was given at longer intervals, but apparently this longer spacing could not convert the aberrant conduction to normal, for he was never found in the latter on such a régime. After the second mecholyl-atropine experiment, quinidine was able to cause conversion to the normal conduction pattern. Just before he was discharged from the hospital, the patient had a bout of tachycardia which terminated spontaneously before any more than a four-lead electrocardiogram could be made. See figure 6 for tracings made during and immediately after this attack.

Case 2. The second patient was 26 years of age. He stated that he had begun to have bouts of palpitation, associated with shakiness and dizziness, five years before he came under our observation. These attacks usually occurred in the latter part of the day, when he was tired from his work, and were usually relieved by merely resting for about 20 minutes. They continued intermittently for about one year and disappeared thereafter under a régime of lighter work and long rest periods. However, following induction into the Army and resumption of a more strenuous physical program, the bouts returned during exertion and were also associated with considerable precordial pain. Physical and roentgenographic examinations disclosed no abnormalities. His blood pressure was 130 mm. Hg systolic and 76 mm. diastolic; sedimentation rate 11 mm. and 5 mm. in one hour; circulation time 12 seconds; serologic reactions, blood count and urinalysis normal.

His electrocardiogram showed the typical characteristics of the short P–R interval and prolonged QRS complex. The P waves were upright; P–R 0.10 second; QRS 0.16 second; deep S in Lead I; tall, slurred, upright complex in Leads II and III; depressed ST–T segments in all. Carotid pressure, alternately over both sides, produced no change in the tracings. The atropine, quinidine-atropine, and mecholyl-atropine experiments previously described in case 1 were repeated without effecting any marked change in the characters. Quinidine caused temporary increase in slurring, slight rounding of the ST–T segments, and slight slowing in the rate. Mecholyl caused increase in the rate, but this slowed after atropine. Digitalis in huge doses (53 c.u. in nine days) had little effect clinically, and did nothing to the tracings except to depress further and round the ST–T segments. In short, the existing time ratios of the P–R and QRS characters remained unaltered throughout all manipulations.

Comment

Wolferth and Wood object to the Wolff, Parkinson and White hypothesis of bundle branch block because "patients who have both normal and abnormal complexes are likely to show the same interval between the beginning of the P wave and the end of the QRS complex in both." Roberts and Abramson also agree with this objection since, in their case, the P–S distance in both abnormal and normal tracings was practically the same—0.274 to 0.279 second. The findings in our work also deny the bundle branch block theory, but on different grounds. When a bundle branch block exists, its P–S interval is longer than the normal. The P–S distance in the abnormal conduction pathway in the first case showed a time interval of 0.20 second, and in the normal (under influence of quinidine) of 0.24 second, at practically all speeds. During the paroxysm of supraventricular tachycardia, however, the P–S was 0.08 second, and quickly thereafter returned to 0.20 second with reversion to aberrant conduction and cessation of the paroxysm. In

the second case, the P–S interval remained at 0.26 second under all circumstances.

The Hunter-Papp-Parkinson hypothesis of partial dislocation of the pacemaker from the sinoauricular node, and interference with the normal ventricular complex by a premature beat arising low in one bundle branch is very unpredictable. It is dependent upon a similarly abnormal expectation that the two impulses constantly maintain a sequential time relationship with each other, for short or long periods of time, at every possible total speed, and during any other mechanism of the heart. However, anything which would change the regular firing of the impulse from the auricle would not necessarily interfere with the lower impulse, and there should then appear an imprint of the latter at a varying relationship with the former. Each total complex should, therefore, differ in contour and time relationship. This is not borne out, however, by a perusal of our record made under the influence of full dosage of digitalis, in which an arrhythmia was produced, but in each beat the QRS complex follows sequentially the P wave without any variation. Even a dissimilar beat in Lead III shows the same relationship of waves and times as in the remainder of the tracing. Again, under the influence of various other drugs used, or mechanical means tried, to alter the complexes, the same P : QRS appears. In the works of Roberts and Abramson and of Moia and Inchauspe,[26] and very recently in that of Clagett,[17] there are tracings in which the patients, without any treatment, showed a spontaneous transition from the abnormal complex to alternate groupings of abnormal and normal complexes. Here, too, there was no disturbance of the P–QRS relationships in alternate complexes or in sequential complexes—a feat truly remarkable if this were left to the chance mechanism suggested by Hunter et al.

Against the theory of functional bundle branch block with auriculoventricular nodal rhythm is (*a*) the maintenance rate of the heart in our patients, which is about double that usually found in this type of retrograde conduction, (*b*) the complete independence of these hearts of vagus stimulation and inhibition, and (*c*) the freedom from digitalis influence of the time intervals of the individual elements of the electrocardiograms. These facts reason against any possibility of hyperirritability of the junctional tissue which would be expected in auriculoventricular nodal rhythm, and point rather to a state in which the tissue and node are more refractory to stimulation than usual.

As for the hypothesis of Holzmann and Scherf, later reiterated by Cossio et al., that the auricular systole mechanically excited a hyperirritable focus in the ventricle, the best answer is forwarded first by Wolferth and Wood,[8] who point out that such a phenomenon "has never been observed in patients with heart block, and never been achieved experimentally, nor ever observed or produced in animals." No further conflict on this point can arise following the animal experimental work of Butterworth and Poindexter, who

could cause the inscription of tracings of the short P–R interval and prolonged QRS complex by applying the input electrode at any point in the auricle and the output electrode at any site in the ventricle. According to this, all points in the ventricle were hyperirritable, which would, therefore, negate the hypothesis.

Several observers have shown tracings in which the character of the P wave is altered in certain complexes, notably before the aberrant ones and before occasional extrasystoles. In addition, there has appeared a change in the P–R time interval. The explanation seems to be readily supplied by the anatomical evidence that the sinoauricular node is made up of an extensive network of interlacing fibers, from any part of which the impulse may originate, the closer to the ventricle, the shorter the P–R interval and the more apt is the P wave to vary from the normal. In their animal experiments, Butterworth and Poindexter could regulate the length of their P–R intervals by lessening or increasing the distance of the input electrode of their amplifier from the region of the sinoauricular node. Furthermore, with the recent demonstration of Wood et al., of at least three muscular bridges connecting the auricle and ventricle in the heart of a patient who had the abnormal conduction pattern, it is very possible that all were capable of conduction, and from varying distances from the sinoauricular node. This would very easily account for minor changes in the P–R interval and P wave in other cases. In our tracings made when the patient was thoroughly digitalized (figure 3), there appears in Lead III one abnormal beat simulating the character of those found in Lead II, which probably represents an impulse from another focus, and may, therefore, be interpreted broadly as an extrasystolic auricular beat. This shows a P wave just like the others, P–R, QRS, and a total P–T interval of exactly the same length in each beat. In this example, it is possible that the digitalis prevented the shortening of the P–R interval.

Concerning the ventricular portion of the tracings, the most frequently reported type is that resembling left bundle branch block, although graphs of right bundle branch block, as in our second case, and of intermediate stages of partial intraventricular block have also been demonstrated. Pardee [27] raised an element of doubt as to the existence of an auriculoventricular accessory pathway which could cause the inscription of an electrocardiogram of the type of the right bundle branch block. Wolferth and Wood considered the right ventricle as the site for the completion of the short-circuiting pathway, later revised their opinion and concluded that the accessory conduction tract led directly to the left ventricle, and recently examined a heart in which the connections were as they originally stated. However, the experimental findings with amplification of Butterworth and Poindexter seem to answer these equivocations, for they reported that with the input electrode in the region of the sinoauricular node and the output electrode on the right ventricle, curves of left axis deviation were inscribed (this is in accord with the

electrocardiographic findings in the above mentioned heart), and that with the output electrode on the left ventricle, tracings of right axis deviation were obtained. It is reasonable to expect that the bizarre conduction pattern may establish a fixed pathway across any of the myoneural bridges connecting the auricles and ventricles in the auriculoventricular groove that were found by Kent, and by Glomset and Glomset, and by Wood et al. anatomically.

To this point, all the theories except the one presented by Wolferth and Wood have been briefly discussed. Very little can be culled from the writings antagonistic to the accessory pathway hypothesis, and all objections that have been raised to it are overcome in an analysis of such contrary evidence. Pardee's question as to the existence of a pathway to produce a configuration of right bundle branch block is anatomically answered by the findings of Glomset and Glomset, and by Wood et al., and experimentally, by the amplifier work of Butterworth and Poindexter. This similarly eliminates Tung's objections as to extra-auriculoventricular connections and impulse transmission. Hunter, Papp and Parkinson denied its accuracy, partly, on grounds of inconstancy of the contour of the P wave and variation in that of the major complex. Wolferth and Wood have held, however, that the contour of the P wave is constant. Butterworth and Poindexter have experimentally found it to be constant. In any event, it is not actually important in interpretation of the mechanism of ventricular stimulation. Any variation may further be interpreted as effects of the manoeuvers and drugs given to study the reactions of the stimulation and inhibition of the sympathetics and parasympathetics. In our own study the reactions are similar, and this deduction is likewise borne out. The argument that Hunter et al. presented regarding the fact that only two types of QRS should be present if the accessory pathway theory is correct—one for the aberrant conduction and one for the normal conduction, with no intermediate types—has been similarly answered by Wolferth and Wood as representing degrees of inverse variation in conductivity of the accessory tract and the bundle of His, and a shifting pacemaker from a focus in proximity to the sinoauricular node to one at a lower level, nearer the auriculoventricular node. Our tracings made during and immediately after a paroxysmal attack show this shift in Lead III, as the heart was apparently recovering from the tachycardia and reassuming the "normal" aberrant pathway of conduction. However, there was an omission of the intermediary type of the QRS in the sudden change from abnormal conduction to the normal under the influence of quinidine.

On the cause of the tachycardia, an interesting theory was first presented by deBoer [28] in 1923. He suggested the existence of an auriculoventricular bundle which formed one link in a path over which a continuous movement of the impulse proceeded from auricle, to bundle of His, to ventricle, to bundle of Kent, to auricle, etc. The hypothesis of Wolferth and Wood is similar, and Butterworth and Poindexter provide the experimental evidence

in their ability to produce a supraventricular tachycardia of about 300 beats per minute by reversing their amplified current from ventricle to auricle in the abnormal pathway. As to the occasional occurrence of paroxysmal ventricular tachycardia, Wood et al.[4] point out that "a premature reëntry into ventricular tissue might initiate an abnormality of the ventricular mechanism, just as premature reëntry into auricular tissue might initiate an abnormality of the auricular mechanism."

From the foregoing, it becomes evident that recent anatomic and experimental evidences have been presented in favor of a theory of conduction which is primitive in nature and philogenetically understandable. Its common electrocardiographic expression goes hand in hand with the equal rarity of occurrence of the clinical syndrome. The proposition of the existence of an accessory pathway has stood the critical investigation of interested workers longer than the other varying theories have, and at present, it is the most inclusive and comprehensible one of all. Further examination of the postmortem findings of these interesting rare anomalies should define, with exactness, the clinical interpretations that have tested the imagination of the reporters of this syndrome.

Conclusions

Anatomical, physiological and experimental evidence is accumulating in favor of the accessory pathway hypothesis as an explanation of the syndrome of benign paroxysmal tachycardia with short PR interval and prolonged QRS complex.

Some variations from previous findings are presented in the cases studied that differ with or lend credence to the accumulated evidence.

Vagal stimulation and inhibition were ineffectual in abolishing the abnormal conduction pattern, as were also all drugs used to stimulate or depress the sympathetic and parasympathetic nervous systems in general.

In one case quinidine sulfate was the only drug which was able to cause abrupt change from abnormal to normal conduction, and on one occasion this too failed, following the subjection of the patient to acetyl-beta-methylcholine chloride and atropine.

Digitalis was incapable of converting the impulse from the unusual pathway to the normal even in full doses.

Maintenance of normal conduction by means of quinidine is unnecessary in these cases unless other factors involving organic or functional changes in the heart occur as the result of continued tachycardia.

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CHOLINE AS AN ADJUVANT TO THE DIETARY THERAPY OF CIRRHOSIS OF THE LIVER*

By A. H. Russakoff,† M.D., and Harold Blumberg, Sc.D.,
Baltimore, Maryland

The past several years have seen a change in the treatment of portal cirrhosis of the liver, particularly in regard to the rôle of diet in therapy. This is especially true of alcoholic cirrhosis, the type which constitutes a majority of the cases of cirrhosis observed in the United States (Ratnoff and Patek [1]). The change has been brought about by experimental and clinical observations.

Connor [2, 3] emphasized the importance of prolonged fatty infiltration of the liver in the development of cirrhosis in diabetes and in chronic alcoholism. Experimental support for this theory was found in 1938 when Chaikoff, Connor, and Biskind [4] observed cirrhosis in depancreatized dogs long maintained with insulin, and Connor and Chaikoff [5] produced cirrhosis in dogs that had been fed a high fat diet and alcohol. The primary etiological importance of diet, rather than alcohol, was subsequently indicated by the production of cirrhosis in rats fed high fat, low protein diets (Blumberg,[6] Blumberg and Grady [7, 8]) and in dogs fed a high fat diet without alcohol (Chaikoff and Connor,[9] Chaikoff, Eichorn, Connor, and Entenman [10]).

In 1939 György and Goldblatt [11] reported two instances of fibrosis and two instances of localized cirrhosis in a large group of rats on diets deficient in parts of the vitamin B complex. Rich and Hamilton [12, 13] produced in rabbits a diffuse portal cirrhosis, resembling Laennec's cirrhosis in man, and associated this effect with the absence of yeast. The respective approaches of high fat diet and nutritional deficiency in the rat were brought closer together by reports of hepatic damage (necrosis, cirrhosis) on moderately high fat, low protein, choline deficient diets to which the addition of choline with yeast or with cystine had a beneficial effect (György and Goldblatt [14, 15]), and through the prevention by choline of a fatty cirrhosis produced by high fat, low protein, choline deficient diets (Blumberg and Grady,[16] Blumberg and McCollum [17]). Cirrhosis was also produced on low protein, choline deficient diets that were low in fat, and prevention was secured by the addition of choline (Lillie, Daft, and Sebrell,[18] Daft, Sebrell, and Lillie [19]). Betaine hydrochloride, which is closely related chemically to choline, was also used to prevent cirrhosis in rats (Webster [20]). Cirrhosis was produced in rabbits on diets in which choline deficiency was not believed to be a factor (Spellberg and Keeton,[21] Spellberg, Keeton, and Ginsberg [22]); however,

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From the Medical Service, Sinai Hospital (A.H.R.), and the Department of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University (H.B.)
† Formerly Resident in Medicine, Sinai Hospital, Baltimore, Maryland; now Assistant Surgeon (R), U. S. Public Health Service.

under different conditions and with a purified diet, a retarding or preventive action in rabbits was found (Blumberg, Mackenzie, and Seligson [23]). A beneficial effect of choline was observed in dietary cirrhosis of dogs, although the preventive action was not complete (Fouts [24]).

The effectiveness of choline in removing fat from the liver was discovered by Best, Hershey, and Huntsman [25, 26] in 1932. Presumably the beneficial or preventive action of choline in experimental cirrhosis is due to this lipotropic activity, although some other mechanism, perhaps affecting cystine metabolism, may also be involved. It has been demonstrated that cystine may produce a non-fatty portal cirrhosis in rats when fed at the excessive, toxic levels of 5 or 10 per cent of the diet (Earle and Victor [27]).

Beneficial or protective action in rats was also secured with high levels of protein (casein),[15, 19, 20, 23] as well as with moderate amounts of the amino acid, methionine,[17, 19, 15, 23] the choline precursor in which casein is relatively rich. Large amounts of yeast, which contains choline, have also been found to be protective,[14, 23] although it must be noted that samples of yeast vary considerably in choline content and sometimes may have only very small amounts. Large amounts of casein have also proved protective in dogs.[24]

Dietary treatment cannot be expected to "cure" experimental cirrhosis in the sense of removing the fibrosis. However, the excellent experiments of Lowry, Daft, Sebrell, Ashburn, and Lillie [28] demonstrated that oral therapy with choline or with large amounts of casein can arrest the cirrhotic process in rats, as indicated by survival, improved general condition, regression of fatty changes and decrease in liver size, and improved appearance of liver cells. Arrest of the cirrhotic process has also been obtained with methionine therapy (Blumberg [29]).

Renewed clinical interest in the dietary management of cirrhosis was stimulated in 1937, when Patek [30] reported that patients with alcoholic cirrhosis appeared to benefit significantly from a generally nutritious, high vitamin diet. These preliminary findings were extended by Patek and Post [31] and Patek [32] in their subsequent study of a series of 54 cirrhotic patients who received a highly nutritious diet (including ample protein) supplemented by concentrates of the vitamin B complex. Fleming and Snell [33] (also Snell,[34] Butt and Snell [35]) likewise observed a favorable influence of diet in a group of 50 patients who received large amounts of vegetable proteins, carbohydrates, and vitamins. In connection with their studies on the treatment of alcoholic neuropathies, Goodhart and Jolliffe [36] and Wayburn and Guerard [37] mentioned incidental improvement in the general condition of some of the cirrhotic patients during the treatment with thiamine and vitamin B concentrates.

From pathological observations there is evidence that hepatic cirrhosis is associated frequently with extensive fatty infiltration of the liver (Connor,[2, 3] Keefer and Fries [38]). From chemical analysis of autopsy material, it is indicated that many cirrhotic livers have a greatly increased content of

neutral fat (Ralli, Paley, and Rubin,[39] Thannhauser and Reinstein[40]), the type of lipid upon which the lipotropic action of choline is very effective. In animal experiments it has been shown that choline has a beneficial effect in the prevention or treatment of certain types of dietary fatty cirrhosis. In view of these pathological, chemical, and nutritional data, it seemed desirable to investigate the possible value of choline as an adjuvant to the dietary treatment of clinical cirrhosis of the liver. While this study was progressing, Broun and Muether[41] published an abstract on the favorable effect of choline in four cases of cirrhosis. Our experience with the use of choline and dietary therapy has been sufficiently encouraging to warrant a report of the results in 10 patients studied during the past two years.

Case Reports *

Case 1. T. P., a 41 year old, white, married female with a long history of alcoholism and dietary insufficiency, was admitted to the Sinai Hospital on June 20, 1942, because of jaundice and persistent bleeding from tooth sockets following the extraction of several teeth. In the recent past she had noted numbness of the extremities, edema of the legs, gnawing epigastric pain, transient jaundice, dyspnea on exertion, and swelling of the abdomen. On admission the temperature, pulse, and respirations were slightly elevated. She was dyspneic, orthopneic, icteric, "nervous," and mildly confused. The tongue was beefy red, and despite attempts at local hemostasis, blood continued to ooze freely from the tooth sockets. The face was covered with telangiectatic lesions, and over the upper chest and arms there were numerous spider angiomata. Pitting edema extended from the legs up to the costal margins. The heart and lungs were essentially normal. The abdomen was markedly distended with fluid, and the abdominal wall was traversed by an extensive superficial collateral venous pattern. The spleen could not be felt, but the liver edge was tender and ballottable six fingers'-breadth below the right costal margin. There were gross tremors of the upper extremities, with paresthesia and hyporeflexia of the lower extremities.

The hemogram on admission revealed a moderately severe anemia. The leukocyte count rose from 10,000 per cu.mm. to 25,000 per cu.mm. within the first few hospital days. Other initial laboratory data revealed a greatly prolonged prothrombin time, an icterus index of 50, a marked bromsulfalein retention, and poor hippuric acid excretion, but normal values for the blood urea, serum proteins, albumin-globulin ratio, and serum cholesterol and esters. The serological test for syphilis was negative.

The patient was transfused and given a vitamin K preparation intravenously in large amounts, with a gradual cessation of gingival bleeding as the prothrombin time became less prolonged. A preparation of vitamin B complex (containing thiamine, riboflavin, nicotinic acid, and pantothenic acid) and various fractions thereof were administered parenterally in massive dosage. The patient was able to take but small quantities of the prescribed high protein, high carbohydrate, low fat diet. One week after admission the patient had a generalized convulsion and lapsed into coma. During the ensuing days the course was ingravescent. She remained comatose for days, with rare momentary remissions of semistupor. The icterus index rose to 200, the blood urea rose to 200 mg. per cent, the serum proteins fell to 5.6 gm. per cent with a

* With the exception of the omission of two cases with proved primary malignancy of the liver, these case reports represent an unselected series of patients with decompensated portal cirrhosis admitted to the Medical Wards of the Sinai Hospital of Baltimore from May, 1942, until December, 1943.

serum albumin of 2.8 gm. per cent, and the serum cholesterol fell to 89 mg. per cent, with esters of 80 mg. per cent. The edema became generalized, and signs of bronchopneumonia and myocardial insufficiency were manifest.

Twenty-five days after admission, while still uremic, cholemic, and in heart failure complicated by bronchopneumonia, the patient was started on tube-feedings of skimmed milk, egg white, glucose, and vitamins A and D. For lack of definite information as to the human adult oral dosage, we began to give 2.0 grams of choline chloride daily in divided doses. Within a few days it was noted that the patient became lucid and mildly conversational at rather frequent intervals. By the eighth day of this regimen, the edema of the upper extremities had disappeared completely and the patient had begun to ask for additional nourishment. The ascites diminished considerably, although the patient had never had an abdominal paracentesis. The serum proteins on this eighth day were 6.7 grams per cent with a serum albumin of 3.9 grams per cent. On the twelfth day, with further clinical improvement, the serum proteins had risen further to 7.6 grams per cent with a serum albumin of 4.5 grams per cent and the serum cholesterol was 175 mg. per cent with esters of 148 mg. per cent. The clotted blood at this time was found to be grossly lipemic. On the thirteenth day after the initiation of this regimen, the patient lapsed into severe pulmonary edema and died.

Postmortem examination revealed less than 200 c.c. of free fluid in the abdominal cavity. The liver was large and presented the gross and microscopic picture of advanced portal cirrhosis. The lungs were edematous and showed foci of bronchopneumonia. In addition, there was chronic cholecystitis with cholelithiasis.

Although this advanced case of cirrhosis terminated in death, the striking improvement subsequent to the administration of choline stimulated further testing of choline therapy.

Case 2. L. S., a 43 year old, white, divorced, female patient with a long history of alcoholism and dietary insufficiency, was admitted in May, 1942. Four months before admission, she had a hematemesis followed by melena and jaundice. Ascites appeared one week later and persisted thereafter. Liver function tests at that time were abnormally low, and esophageal varices were demonstrable. The serum proteins were 6.1 grams per cent with a serum albumin of 4.2 grams per cent. The serological test for syphilis was negative. She was treated for a month with a high carbohydrate diet, mercurial diuretics, and repeated abdominal paracenteses without improvement. During this regimen, spider angiomata and chloasmic lesions appeared.

She was readmitted in July, 1942, for a test with choline. Physical examination at that time revealed the common stigmata of decompensated portal cirrhosis, the liver and spleen extending three fingers'-breadth below the costal margins. There was a normochromic anemia with a leukopenia. For two weeks the patient was treated with a high protein, high carbohydrate, low fat diet without clinical improvement. Liver function tests showed no laboratory evidence of improvement. Choline chloride was administered then in doses of 0.5 gram thrice daily, and on the fourth day the patient began to lose weight. During a period of 30 days the patient's weight dropped from 157 to 134 pounds, in association with a diminution in abdominal girth of five inches and the complete disappearance of ascites.

On follow-up examinations over a period of 18 months, the patient has remained free of ascites, the serum proteins have risen to 7.4 grams per cent with a serum albumin of 5.0 grams per cent, the skin lesions have waned, the spleen has receded to the left costal margin, the liver is smaller, the blood picture is normal, esophageal varices are no longer demonstrable, there has been a return of the normal menstrual cycle after almost a year of complete amenorrhea, and the patient has remarried happily. She has continued on the prescribed diet and choline, and has abstained from alcohol except socially.

Case 3. L. G., a 57 year old, married housewife, with a history of alcoholism, was admitted in July, 1941, because of dyspnea following the passage of a tarry stool. She was found to have a hepato-splenomegaly, ankle edema, and a marked secondary anemia. On bed rest and a high carbohydrate diet, the edema disappeared, she lost 20 pounds, and she was discharged improved. She was readmitted one year later with ankle edema, ascites, hepato-splenomegaly, and anemia. Liver function tests were below normal, and the serum proteins were 5.6 grams per cent with a serum albumin of 3.3 grams per cent. The serological test for syphilis was doubtful on a few occasions, but negative on many others. Serological tests for syphilis on the spinal and ascitic fluids were negative, and there were no stigmata of syphilis.

The patient was treated for two weeks with a high protein, high carbohydrate, low fat diet without benefit. During this period an abdominal paracentesis was necessary. Choline chloride was begun in doses of 0.5 gm. four times daily. During the succeeding three weeks the edema and ascites disappeared, and there was an associated loss of weight, a diminution of girth, and a feeling of well-being. She was discharged markedly improved on diet and choline.

On monthly follow-up examinations, the patient continued to improve. There was no recurrence of ascites; there was improvement in the liver function tests, associated with a rise in serum proteins to 7.1 grams per cent with a serum albumin of 4.9 grams per cent, and a remarkable increase in energy.

After six months of good health, the patient resorted to alcohol again, took an inadequate diet, and ceased to take choline regularly. She returned to the hospital but was uncoöperative and left against advice. She died at home several weeks later.

Case 4. E. P., a 27 year old, white, married housewife, with a long history of alcoholism and dietary inadequacy, gastrointestinal disturbances, recurrent icterus, neuritis, and non-traumatic epistaxes, was admitted in December, 1942, because of increasing jaundice and abdominal distention.

She was found to be anemic, was deeply jaundiced, showed evidence of thiamine, riboflavin, and nicotinic acid deficiency. She had an inactive mitral valvulitis. The abdomen was greatly distended with free fluid. The liver edge was palpable five fingers'-breadth below the right costal margin, and splenic dullness was increased. There was edema of the lower extremities.

The hemogram revealed a macrocytic hyperchromic anemia, with a leukocytosis and a shift to the left. The serological test for syphilis was negative. The blood urea and non-protein nitrogen were normal, the icterus index was 100, the prothrombin time was prolonged, the bromsulfalein retention 40 per cent, the serum cholesterol 73 mg. per cent with esters of 29 mg. per cent. and the serum proteins were 8.2 grams per cent with a serum albumin of 5.1 grams per cent.

The patient could not tolerate the prescribed diet. Two abdominal paracenteses were performed, and generous supplements of a vitamin B complex preparation and of a vitamin K preparation were given parenterally. Choline chloride was administered in doses up to six grams daily. Nevertheless, she developed signs of bronchopneumonia, lapsed into pulmonary edema, and died on the fifth hospital day.

Autopsy revealed portal cirrhosis of the liver with splenomegaly, ascites, and esophageal varices. There was evidence of an inactive mitral valvulitis, pulmonary edema, and bronchopneumonia. The pathologist stated that microscopic sections of this liver showed fat throughout the entire hepatic parenchyma.

Case 5. J. C., a 53 year old, non-alcoholic, white male, was admitted in February, 1943, because of abdominal swelling. His past history was of significance in that he had been treated with duodenal drainage for a condition about which he remembered little, some 25 years before admission, and that for years he had been on a diet grossly deficient in protein. About eight months before admission he developed abdominal swelling associated with weakness, dyspnea, and ankle edema, but he had

no gastrointestinal complaints or jaundice. He had recently been in another local hospital where he had been tapped and treated with a "nutritious" diet without benefit. Physical examination revealed an anemic, malnourished man who showed no signs of vitamin deficiency. The protuberant abdomen was traversed by dilated superficial veins; there was a demonstrable fluid wave and shifting dullness. The liver edge was found to be high under the right costal arch after abdominal paracentesis, and the spleen extended two fingers'-breadth below the left costal margin. Routine liver function tests were abnormally low, the serum proteins were 6.0 grams per cent with a serum albumin of 3.0 grams per cent, and the serological test for syphilis was negative.

Because of the marked abdominal distention, it was necessary to perform several abdominal paracenteses to afford the patient sufficient comfort to tolerate the prescribed high protein, high carbohydrate, low fat diet. Since the patient seemed to be getting worse clinically after a few weeks on diet alone, the serum proteins having fallen to 5.8 grams per cent with a serum albumin of 2.7 grams per cent, it was decided that choline chloride should be administered in doses of 4.5 grams daily. After two weeks the total proteins had risen to 6.5 grams per cent with a serum albumin of 4.2 grams per cent, and no further abdominal paracenteses were necessary. After 40 days of this therapeutic regimen, the serum proteins were 6.7 grams per cent with a serum albumin of 5.0 grams per cent. Associated with this response there was a diminution in the amount of ascites and a decrease in weight of 11 pounds. He was discharged markedly improved on diet and choline, but still had a small amount of ascites.

On follow-up examinations for nine months, his general health and nutrition were even better than on discharge. The amount of ascites had diminished slightly. He was at work and able to support his family again. He continued faithfully on diet and three grams of choline daily, and in December, 1943, the serum proteins were 7.0 grams per cent with a serum albumin of 5.4 grams per cent.

Case 6. R. W., a 56 year old, white bartender, with a history of alcoholism and periodic abstinence from food during a period of 20 years, was admitted in October, 1942, because of edema of the legs and swelling of the abdomen of several months' duration. On physical examination he was found to be sub-icteric and to have a left hydrothorax and ascites. The liver edge extended four fingers'-breadth below the right costal margin, and the spleen was easily palpable after abdominal paracentesis. There was marked pitting edema of both lower extremities and clubbing of the fingers.

The hemogram revealed a moderate normochromic anemia with a normal leukocyte and differential count. The serological test for syphilis was negative. Liver function tests were below normal, with serum proteins of 6.6 grams per cent and a serum albumin of 4.8 grams per cent. Tremendous esophageal varices were demonstrated.

The patient was tried on the adopted dietary regimen alone, but required repeated abdominal paracenteses to afford him sufficient comfort to tolerate food. Choline chloride was administered in doses up to five grams daily without demonstrable clinical improvement. Although he lapsed in and out of cholemia, the serum proteins rose to 7.2 grams per cent with a serum albumin of 5.0 grams per cent. Five weeks after admission, the patient had a lethal hemorrhage from a ruptured esophageal varix.

Autopsy showed a large but non-fatty cirrhotic liver, containing many extraordinary dense fibrotic sheets associated with an extensive collateral circulation about the lower end of the esophagus. There were also ascites, hydrothorax, splenomegaly, chronic cholecystitis, and cholelithiasis. From the gross and microscopic appearance of this liver, there was little that could have been expected therapeutically of lipotropic substances.

Case 7. A. W., a 58 year old, white male with a history of alcoholism, was

admitted in December, 1941, with ascites and ankle edema. A few years previously he had been found to have an enlarged liver and a positive serological test for syphilis, but subsequent examinations of blood and a spinal fluid examination were all negative for syphilis.

On physical examination, in addition to marked ascites, an extensive superficial abdominal collateral circulation, and edema of the legs, the patient was found to have an inactive mitral valvulitis with chronic auricular fibrillation, but without evidence of a constrictive pericarditis. The blood picture, the serum proteins, and serum albumin were normal. Studies of the ascitic fluid were negative for specific disease.

He was treated with a high carbohydrate, salt-free diet, vitamins, digitalis, mercurial diuretics, and abdominal paracenteses with only slight improvement. After abdominal taps, the liver edge was felt high under the right costal margin. The spleen was never felt. He was discharged on the forty-fifth hospital day.

He was readmitted nine months later, having adhered to the prescribed regimen without improvement. Abdominal paracenteses, averaging approximately 10 liters each, were necessary every four weeks. The physical findings were unchanged. The hemogram was normal, the bromsulfalein retention was 20 per cent in 30 minutes, and the serum proteins were 5.2 grams per cent with a serum albumin of 2.2 grams per cent.

In addition to digitalis, the patient was given a high protein, high carbohydrate, low fat diet supplemented with six grams of choline chloride daily. On this regimen during the 90 day hospital stay and during the subsequent 90 day follow-up period, the serum proteins rose to 6.5 grams per cent with a serum albumin of 4.6 grams per cent, and the bromsulfalein retention dropped to 5 per cent in 30 minutes. Nevertheless, he required six abdominal paracenteses.

Because the osmotic factor had been well cared for and the cardiac status was of minor import, we felt that the shrunken liver might exert a mechanical effect and thus be the major cause of the recurrences of ascites; so the patient was readmitted in May, 1943, for a sapheno-peritoneal anastomosis. A unilateral anastomosis was performed under local anesthesia by Dr. Louis J. Kolodner. The procedure was well tolerated, and during the past six months the patient has continued on the prescribed diet and 4.5 grams of choline daily. The serum proteins have risen further to 7.4 grams per cent with a serum albumin of 5.2 grams per cent and the patient has required only two abdominal paracenteses.

Case 8. V. W., a 62 year old, white, male alcoholic, was admitted in June, 1943. He had been well until one month before admission, when he noted jaundice, a change in the character of his stool, weight loss, ankle edema, and swelling of the abdomen. On physical examination he was obviously icteric, the abdomen was distended with fluid, and after abdominal paracentesis the liver edge was felt three fingers'-breadth below the right costal margin. The spleen was not palpable. Edema was marked over the legs, and extended over the abdominal wall and sacrum.

There was a macrocytic hyperchromic anemia with a normal leukocyte and differential count. The serological test for syphilis was negative. Routine liver function tests were far below normal, the serum proteins were 5.8 grams per cent with a serum albumin of 3.9 grams per cent, the icterus index was 50, and esophageal varices were demonstrable in the esophogram.

On dietetic treatment alone the patient fared poorly, requiring abdominal paracenteses. Choline chloride was begun in doses of four to six grams daily, but the effect was not striking at first, for the patient required another abdominal tap. From this time until his discharge 45 days later, the patient improved steadily. The edema, ascites, and icterus disappeared, but the serum proteins and serum albumin were not altered appreciably. Nevertheless, the hemogram became normal without

transfusions, the esophageal varices were no longer demonstrable, and the bromsulfalein retention was 0 per cent in 30 minutes.

When seen on follow-up examinations, the patient had continued to improve, the serum proteins had risen to 7.6 grams per cent with a serum albumin of 5.2 grams per cent, and the patient was about to go back to work.

Case 9. O. B., a 31 year old, white, divorced female with a long history of alcoholism and dietary inadequacy, was admitted in September, 1943, with the diagnosis of pneumonia and decompensated cirrhosis of the liver. For more than a year before admission she had gastrointestinal complaints, transient jaundice, swelling of the abdomen, bleeding hemorrhoids, non-traumatic epistaxes, aberrations of the menstrual cycle, and symptoms of polyneuritis. Her weight prior to admission was approximately 155 pounds.

On admission the temperature was 104° F. (r), the pulse 136, the respirations 38, and the blood pressure 150 mm. Hg systolic and 95 mm. diastolic. The patient was dyspneic, cyanotic, edematous, and deeply icteric. She was slightly confused, and had a coarse tremor, the mousey odor of cholemia, and signs of consolidation of the lower lobe of the left lung associated with a diffuse bronchitis. The distended abdomen was traversed by an extensive collateral venous anastomosis, and showed shifting dullness and a fluid wave. The liver edge was nodular, tender, and extended nine fingers'-breadth below the right costal margin. The spleen was not palpable, but there were tenderness and increased splenic dullness in the left flank.

The hemogram revealed a mild normochromic anemia with a normal leukocyte and differential count. The serological test for syphilis was negative. The icterus index was 100, and there was a 55 per cent retention of bromsulfalein in 30 minutes. There was a moderate hypercholesterolemia with maintenance of a normal ester ratio. The serum proteins were 6.3 grams per cent with a serum albumin of 4.5 grams per cent. The urea, non-protein nitrogen and prothrombin times were normal, and the serum phosphatase was 10.5 Bodansky units.

A type IX pneumococcus was found in the sputum, and the patient was given oxygen and sulfadiazine in appropriate dosage for eight days without a notable response. Consequently, the sulfadiazine was stopped. From the outset, a high protein, high carbohydrate, low fat diet with vitamin supplements was forced. Choline chloride was begun on the third day in doses of 1.5 grams thrice daily. By the twentieth day the patient was afebrile, the pneumonia had resolved, the edema had disappeared, and the ascites had diminished. The serum proteins had risen to 7.0 grams per cent with a serum albumin of 5.1 grams per cent, the icterus index had dropped to 50, and the liver edge had receded to five fingers'-breadth below the costal margin.

Thereafter the patient's course was marked by continued improvement. During the next four weeks she became free of ascites, the icterus index dropped to 14, the bromsulfalein retention was 2 per cent in 30 minutes, and the serum phosphatase was 5.9 Bodansky units. No abdominal paracenteses were necessary, but the patient did receive three transfusions specifically for anemia during her early hospital stay. She was discharged after seven weeks, weighing 136½ pounds. She stated that she had not felt as well in years.

She has been ascites-free for three months and continues to enjoy excellent health. The serum proteins are now 8.5 grams per cent with a serum albumin of 6.2 grams per cent. The liver edge is now two to three fingers'-breadth below the costal margin, and there has been a return of her normal menstrual cycle. She has gained about 10 pounds, and her only complaint is of progressive alopecia, which is considered to be secondary to her severe illness.*

Case 10. L. S., a 35 year old, white, male alcoholic, was admitted in November,

* More recently there has been a return of scalp hair without medication.

1943, because of fatigue and recent swelling of the abdomen. There was a history of polyneuritis and gastrointestinal symptoms. On physical examination the patient was found to have a right hydrothorax, ascites, and a liver extending seven fingers'-breadth below the right costal margin, but no palpable spleen. The weight on admission was 157 pounds.

The hemogram showed a mild anemia. Liver function tests were normal, with serum proteins of 7.6 grams per cent and a serum albumin of 5.2 grams per cent. The serological test for syphilis was negative.

Since the patient was unable to tolerate the prescribed diet, an abdominal paracentesis was performed. Following this procedure, he took his diet well. Because the patient ran a remittent febrile course and was sensitive to high dilutions of tuberculo-protein, studies were carried out on both the pleural and ascitic fluid, which showed no evidence of tuberculosis. Roentgenographic studies of the chest revealed no evidence of tuberculosis or of Pick's disease.

On dietetic regimen alone for approximately three weeks, there was a diminution in the amount of ascites, and the patient's weight declined to and remained stationary at 145½ pounds. Choline chloride was begun in doses of 6.0 grams daily; there followed a further reduction in weight to 139½ pounds associated with less ascites and with a distinct improvement in general nutrition. Ten days after the initiation of choline therapy, the serum proteins were 8.0 grams per cent with a serum albumin of 5.6 grams per cent.

The patient was discharged on diet and choline. He was considerably improved and able to return to work, but still had demonstrable ascites.

In evaluating this group as a whole, and it is recognized that it does not have statistical significance, it is seen that four of this group of 10 patients are dead. Of these four, one died on the fifth hospital day of pulmonary edema complicated by bronchopneumonia (case 4). The extensive fatty infiltration of the liver suggested that much might have been expected therapeutically of lipotropic substances had the case not been complicated. A second patient (case 6), whose enlarged liver at autopsy was markedly scarred with dense sheets of fibrous tissue but contained very little fat, died of an exsanguinating esophageal hemorrhage. We believe that treatment can avail little in such instances in which the fibrotic process has advanced beyond the hope of improvement. Incidentally, this case illustrates that a large cirrhotic liver need not be a fatty liver.

Both of the remaining two deceased patients showed definite temporary improvement. Although the first (case 1) died in pulmonary edema complicated by bronchopneumonia, on the prescribed regimen she rallied briefly from a grave state, with an increase of serum proteins and serum albumin from extremely low figures to normal levels and a disappearance of edema and ascites. The second patient (case 3) died seven months after discharge. During this time she had been free of ascites and enjoyed good health until she resorted again to alcohol and neglected her diet and choline.

Of the six living patients, three have continued to be entirely free of ascites—one for 18 months (case 2), another for six months (case 8), and a third for three months (case 9). All three are rehabilitated to a relatively normal physical state and are adjusting socially. Of the remaining three patients with ascites, all have improved to some extent. One patient (case

7), who has a small shrunken liver and who has had ascites for at least two years, was hypoproteinemic and required abdominal paracenteses every four weeks prior to admission. On the prescribed regimen and a unilateral sapheno-peritoneal anastomosis, he goes 16 weeks without abdominal tapping. A second patient (case 5) has improved remarkably and has been working vigorously for nine months with a persistent small amount of ascites. The third (case 10), who was discharged from the hospital one month ago (December), is greatly improved and able to return to work.

In six instances diet alone was tried for several weeks without benefit. In three of these cases obvious responses were noted within a week after the addition of choline, and probable responses were subsequently noted in two of the other patients.

Discussion

There is a logical basis for the use of choline in the treatment of cirrhosis of the liver. Prior to the revolutionary work of Patek [30] and Patek and Post,[31] the mainstay of a rather hopeless therapeutic regimen was a diet high in carbohydrate and low in protein and fat. In their studies on a large group of cirrhotics, these workers have established firmly the value of a diet high in protein and in vitamins. Fleming, Snell, and Butt [33, 34, 35] have confirmed and adopted their general method. Experimental justification for this thesis is suggested by the work of Ravdin and coworkers (Ravdin, Thorogood, Riegel, Peters, and Rhoads [42]) on the chemical analysis of liver biopsies from surgical patients. Their studies demonstrated the protective effect that high protein diets afford the damaged liver, and also the associated reduction of liver fat. There can now be little doubt that diets rich in protein of high biological value are indicated in the presence of liver damage. The parenteral administration of amino acids in several cases of cirrhosis has been reported by Fagin and Zinn,[43] and evidence to suggest a lipotropic effect from such administration has been published by Fagin, Sahyun, and Pagel.[44] According to Hoagland,[45] soybean lecithin (which contains choline among other things) and parenteral crude liver extract are to be recommended.

There is rather general agreement that the deposition of fat precedes irreversible fibrotic changes in the pathogenesis of some types of portal cirrhosis, notably the alcoholic. It has been established by experiment that choline exerts a lipotropic effect, especially on neutral fat, and thus is capable of mobilizing fat from the fatty liver. On the basis of the aforementioned facts, there is a sound rationale for the use of choline in the treatment of cirrhosis of the liver in man. Indeed, since serious and fatal consequences may result from an enlarged fatty liver even in the absence of fibrosis (Connor,[2] Keefer and Fries,[38] LeCount and Singer,[46] Graham [47]), the use of choline in such cases may prove to be of decided value. It may be noted, incidentally, that Danis and Anderson [48] have observed beneficial effects from the use of choline chloride in three cases of icterus gravis neonatorum, a disorder with which a fatty liver is associated.

Despite the fact that the lipotropic effect of choline has been recognized for more than 10 years, we fail to find a single detailed clinical report on its use in the treatment of cirrhosis of the liver. In recording the efficacy of choline as an adjuvant to the already recommended high caloric, high protein, high carbohydrate, low fat, high vitamin diet on the basis of treating only seven cases with beneficial results, we do so to call attention to what may well be a helpful therapeutic agent; and our experience in the close observation of several patients, who failed to respond to the diet until choline was administered, lends strong support to this view. The possible rôle of another lipotropic substance, inositol (Gavin and McHenry,[49] Gavin, McHenry, and Patterson [50]), is yet to be investigated.

To our knowledge, the first clinical note on the use of choline in human cirrhosis was the abstract by Broun and Muether,[41] who were impressed favorably with their results in four cases. Yater, however, in a discussion [51] expressed a very unfavorable opinion: "During the last year I have used it (choline) perhaps in fifteen cases. Some of these patients went along and died promptly, not because of the choline but in spite of it. Other patients have remained about the same and some have improved. . . . it seems hardly likely to me from these cases and from reading the reports of a few others in which choline has been used that we can expect very much from this form of treatment." On the other hand, Gordon * [52] has stated (personal communication to the authors) that he has observed striking improvement in five cases of alcoholic cirrhosis treated with a combination of choline and cystine.

It is well known that the cirrhotic process may advance to an irreversible stage in which nothing is of much value. That this stage cannot be detected clinically even with the help of liver function tests is common knowledge to those who have had even a limited experience with this disease. Therefore, to condemn choline because improvement has not been observed in some few cases of decompensated portal cirrhosis in which it has been tested is comparable to doubting the efficacy of certain sulfonamides in the treatment of pneumococcal pneumonia because of the poor results noted in cases complicated by an overwhelming bacteremia; for the presence of persistent ascites in cirrhosis may be considered relatively as ominous as a severe sepsis complicating pneumonia. There is need for a study of a large, well-controlled group of cirrhotics and for an intelligent discrimination in appraising individual cases. In general, it seems that those patients having enlarged livers, and probably a fatty type of cirrhosis, will be most likely to respond favorably to choline therapy.

In the treatment of our cases, we prescribed a diet normal or high in calories, high in protein of good biological value (and rich in methionine), high in carbohydrate, and as low in fat as could be prepared easily by the

* Dr. Edgar S. Gordon, University of Wisconsin School of Medicine, Madison, Wisconsin. (Now in Medical Corps, U. S. Army.)

dietitians and tolerated by the patients (C 250–300, P 125–200, F not more than 60). Lean meats, as well as skimmed milk and cottage cheese, were used freely as sources of protein. In several instances after a preliminary period on diet alone, choline was started. At first, due to timidity, small doses were prescribed; later, as much as six grams of choline chloride was administered daily in divided doses. We chose peppermint water as a solvent, for flavoring and for the specific purpose of denying our patients even the small amounts of alcohol present in an elixir. No unfavorable reactions were encountered when choline was administered in this manner after meals. However, when three patients after an overnight fast were given 0.5 gram of choline chloride without food, one experienced nausea without vomiting. This was associated with a very slight drop in blood pressure and a slight slowing of the heart rate. One patient had no untoward effects during the administration of as much as six grams of choline chloride daily for six months.

Our patients received vitamin supplements, although not in the heavy dosage sometimes recommended by others. We gave 1 c.c. of a standard preparation of vitamin B complex parenterally to several patients who had no clinical evidences of deficiency; large doses of the various fractions were administered when indicated. Only one of our patients received powdered yeast, which is an inconstant and at times a very poor source of choline, because the primary purpose of the study was to evaluate the efficacy of choline. Some observers have found crude liver extract beneficial in some refractory cases of cirrhosis. We used none. Vitamin K was given parenterally to all jaundiced patients without regard to the prothrombin time. Non-icteric patients with increased prothrombin time received vitamin K by mouth. One patient received as much as 10 mg. of a vitamin K preparation intravenously several times daily to control bleeding (case 1). We prescribed 15,000 to 20,000 U.S.P. units of vitamin A and 1,500 to 2,000 U.S.P. units of vitamin D daily. No bile salt therapy was used in this group of cases.

Abdominal paracenteses were performed in eight of the ten cases as frequently as was necessary to afford the patient sufficient comfort to take all of his therapeutic diet. This we consider to have been of fundamental importance. Transfusions of whole blood were given in a few instances specifically for anemia.

Improvement was gauged by the clinical response of the patients correlated with alteration of the laboratory data. An increase of the serum proteins, and more specifically of the serum albumin, above the critical level was usually associated with a spontaneous diuresis, a loss of weight, a diminution of girth, the disappearance of edema and ascites, the subsidence of icterus, a feeling of well being, an improvement in appetite, the resumption of the normal menstrual cycle in female patients, and the freedom from the necessity of further abdominal paracenteses except in one case (case 7).

In the patients with hepatomegaly, there usually appeared to be a decrease in the size of the liver. These clinical responses were associated usually with improvement in liver function tests, a diminution in the icterus index, a decrease in prothrombin time, and improvement in the blood picture in those patients who presented abnormalities of one or more of these determinations. The speed of response in those who improved was variable. Three patients responded within a week after the administration of choline was started. Others responded more slowly.

Summary

1. The course of ten patients with decompensated portal cirrhosis of the liver, who have been treated with a high caloric, high protein, high carbohydrate, low fat diet, the usual vitamins, and choline, has been presented.

2. Of the nine patients treated adequately with this regimen, seven improved. Three of these patients manifested little or no change when treated first for several weeks with the high protein diet alone, but showed distinct improvement within a week after the beginning of choline therapy.

3. A review of the literature on the relation of choline to cirrhosis has been presented.

4. There seems to be justification for the use of choline as an adjuvant to the dietary therapy of cirrhosis of the liver, particularly of the fatty, alcoholic type.

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PRIMARY AND SECONDARY MYELOFIBROSIS (A CLINICAL AND PATHOLOGICAL STUDY OF THIRTEEN CASES OF FIBROSIS OF THE BONE MARROW) *

By Lowell A. Erf, M.D., F.A.C.P., and Peter A. Herbut, M.D.,
Philadelphia, Pennsylvania

Myelofibrosis means fibrosis of the bone marrow. The process may be either focal or generalized, primary or secondary, mild or severe, and may or may not be associated with various degrees of myelosclerosis (defined as an excessive proliferation of endosteal bone, known also as osteosclerosis) in any or all bones of the body. Among others, fibrosis of the bone marrow has been observed in the following conditions:

A. Focal:

I. Primary (idiopathic),

1. Such a condition has not been described unless Albright's disease [1] can be considered as such, or
2. Monomelic medullary osteosclerosis [2] (case 1, table 1).

II. Secondary to (in certain cases),

1. Various bone diseases,
   a. Focal osteitis fibrosa.[3]
   b. Various congenital bone diseases.[4, 5]
   c. Paget's disease.[4, 5]
   d. Osteomyelitis (clinical and experimental).
   e. About sites of bone tumors; temporarily about sites of fractures.
2. Albright's disease.[6, 7]
3. The majority of the conditions listed under *B.* "Generalized" and II, "Secondary" may have only associated focal myelofibrosis.
4. Experimental,
   a. Occlusion of nutrient vessels to marrow (not by ligation,[8] but by multiple infarction [9]).
   b. Transplantation of marrow to anterior chamber of eye (see Discussion).

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B. Generalized:

I. Primary (idiopathic),

1. Myelofibrosis [10, 11] (cases 2–6, table 1).
Myelofibrosis has been a prominent feature in many cases described as,

a. Leukanemia (Leube and Arneth [12]).
b. Chronic splenomegaly with anemia and myeloid reaction in the blood (Weil and Clerc).
c. Splenomegaly of myeloid type with myelocythemia (Rathery).
d. Myeloid splenic anemia (Vaquez and Aubertin).
e. Atypical myeloid leukemia or aleukemic myelosis (Hirschfeld).
f. Chronic non-leukemic myelosis (Hickling [12]).
g. Myelosclerosis (Mozer).
h. Osteosclerotic anemia (Rusk and Miles; Chapman).
i. Myelophthisic splenomegaly (Ballin and Morse).
j. Aleukemic myelosis with osteosclerosis (Stephens and Bredeck).
k. Leukoerythroblastic anemia with diffuse osteosclerosis (Mendeloff and Rosenthal).
l. Splenomegaly with myeloid transformation (Tudhope).
m. Marrow sclerosis associated with massive myeloid splenomegaly (Taylor and Smith).
n. Megakaryocytic myelosis with osteosclerosis (Hewer).
o. Generalized osteosclerosis (Parkes-Weber [13]).
p. Hemopoietic splenomegaly with marrow sclerosis (Wade).
q. Myeloid megakaryocytic hepato-splenomegaly (Downey and Nordland).
r. Agnogenic myeloid metaplasia (Jackson, Parker and Lemon [70])

II. Secondary to (in certain cases),

1. Various bone diseases and metastases to bones,

a. Generalized osteoporosis.[14]
Osteogenesis imperfecta cystica.
Infantile scurvy.
Osteomalacia.
Renal rickets.

b. Generalized increased density of bone,[14]
Diffuse fibrosis of bone (often progresses from a porotic to a petrosic condition).
Melorheostosis.
Osteopetrosis.[11]
Leontiasis ossea.
Osteitis deformans (Paget's disease).[14]
Osteitis fibrosa cystica (Von Recklinghausen's disease).

c. Metastases to bone [14, 15, 16, 17, 18] (cases 9–12, table 1),
  a'. Osteolytic (as in cases with cancer of breast or kidney).
  b'. Osteoplastic (as in cases with cancer of prostate and stomach).[58]
  c'. Pagetoid (as in cases with cancer of prostate, stomach, colon or breast).
  d'. Cyst-like (as in cases with hypernephroma or in cases with cancer of the thyroid gland).

2. Myelosclerosis.[19, 20, 21]
3. Myeloma [22] and tumors of bone marrow (case 13, table 1).
4. Polycythemia.[11, 18, 19, 23]
5. Leukemia [10, 11, 12, 18, 24, 69] (case 7, table 1).
6. Hodgkin's disease.[25, 26] (case 8, table 1).
7. Gaucher's disease.[16]
8. Amyloid disease.[16]
9. Xanthomatosis.[6]
10. Erythroblastosis.[27]
11. Septicemia.[11]
12. Renal disease.[7]
13. Poisonings,
  a. Benzene.[28]
  b. Fluorine.[29]
  c. Irradiations; chronic,[30] not acute.[31]
14. Experimental,
  a. Strontium.[32]
  b. Phosphorus.[32]
  c. Estrogens.[33, 34, 35]
  d. Saponin.[36, 37]
  e. Specific antibodies.[36, 38]
  f. Charcoal.[9]
  g. Anterior pituitary extract.[39, 40]
  h. Parathyroid extract and irradiated ergosterol.[41]
  i. Myeloid and lymphoid stimulating substances [42] (See Experimental Discussion and figure 3).

This paper will be limited to a discussion of *generalized* myelofibrosis and particularly to the *primary* or idiopathic type. One case of focal myelofibrosis (fibrosis of the bone marrow with associated excessive osteosclerosis or endosteal thickening) has been included for the sake of completeness and because of the rarity of this condition. A complete discussion of this case has been published elsewhere.[2]

A. Primary idiopathic generalized fibrosis of the marrow was first termed myelofibrosis (see synonyms above) by Mettier and Rusk [10] in 1937.

TABLE I

Case Studies of Myelofibrosis, Both Primary and Secondary, Arranged According to the Classification Presented in the Introduction

Case No.	Name, Sex, Age, Color, Occupation	Date of Admis. Hosp. No.	Chief Complaints (on first admission) and Their Duration	Physical Findings	Laboratory Findings (Essential Findings)	Marrow Puncture Aspirations (Sternal unless otherwise indicated)	Biopsy (Site and Microscopical Diagnosis)	Treatment	Results and Remarks, also Essential Autopsy Findings (See Pathology)
Focal									
I. Primary									
(1)	P. Sil. F.—27—W. Secretary	5-6-39 6-26-39 3-17-42 BH 10205	Pain in entire *right* leg. Worst in right knee.—4 years.	Essentially negative.	X-ray of bones—increased density lower half of *left* femur and upper half of *left* tibia but confined to the medullary canal. Skull—Negative. Bl. Cal.—11.6. Bl. Phos.—3.9. Phosphatase—6.0 Wass.—neg.		7-1-39 *Left* tibia—Myelosclerosis and Myelofibrosis. 8-10-39 Exploratory laminectomy—Fibrosis of ligamentum flavum.	Sedatives and physio-therapy.	Discharged as possible caisson disease—infarction of nutrient vessels to bone. Later considered Monomelic Medullary Osteosclerosis. (See ref. 2.) 1943—Patient quite comfortable. Without pain (Oct. 1944).
II. Secondary	No case study presented								
Generalized									
I. Primary									
(2)	P. Hob. M 35 W Foundry worker	11-9-43 GH 6088	Weakness—6 mo. Bone pains in feet and legs—6 mo. Refractory Anemia—6 mo. Irregular slight fever.	Pallor and possibly slight jaundice. Spleen just palpable. Few ecchymoses.	X-ray of bones—generalized demineralisation and changes in spine suggesting Marie-Strumpell disease. MCV—100. Hematocrit—19. Liver function studies—normal. Wassermann—negative.	One attempt failed. 2nd revealed hypoplasia of marrow elements.	11-29-43 Sternum—Myelofibrosis.	Testosterone 25 mg. daily. i.m. from 12-10-43 to 1-10-44. Brewer's yeast orally. Red blood cell suspensions.	Died 1-31-44. No autopsy.
(3)	E. Lac. F 2 W	7-8-43 GH 1510	Refractory anemia and asso. symptoms, loss of appetite and weight—6 mo. Listless. Slight, irregular fever.	Pallor. Splenomegaly—3 cm. Hepatomegaly—1 cm. Petechiae on both legs.	X-ray—long bones, skull and chest—normal. MCV—87. Hematocrit—27. Bleeding time—slightly increased. Fragility—normal. Wass.—neg. Bilirubin—.1 mg. %.	Two attempts on tibia, one on femur failed. Sternum revealed hypoplasia of all elements.	8-18-43 Rt. tibia—Myelofibrosis.	Liver extract, iron and transfusions apparently failed. Testosterone 10 mg. i.m. 2×weekly—started 12-16-43. Associated with oral yeast extract and con'd until June 1944.	Is more active physically. Partial remission for the 6 mos. preceding Oct. 1 1944.
(4)	J. Lam. M 46 W Carpenter	1-13-44 GH 5437	Tiredness and weakness 4 yrs. Bone pains in legs 4 wks. Jaundice and pallor noticeable for one month.	Pallor. Spleen—8 cm. Liver—6 cm. below costal margin. No lymphadenopathy.	X-ray—increased density of all bones. Bl. Cal.—9.2. Bl. Prot.—3.3. Bl. Phosphatase—10.4 units. Bl. Plasma Prot.—5.7. Wass.—neg. Urinary estrogens—30 Mouse Units/24 hrs.	Sternal puncture—hypoplasia with atypical myeloid cells.	1-15-44 Sternum—Myelofibrosis. (See figure 2.)	Testosterone 25 mg. i.m. daily from 1-25-44 till 3-1-44. From March to Oct. 1944 received 55 red blood cell suspensions.	Clinically comfortable but suspensions required to maintain adequate red blood cell level.
(5)	R. Mar. F 49 W Housewife	6-8-43 GH 294	Refractory anemia and associated symptoms (tiredness, weakness, dizziness)—1 year. Slight irregular fever.	Pallor. Splenomegaly—3 cm. Hepatomegaly—4 cm. No lymphadenopathy.	X-ray—long bones show marked thickening. Sigmoidal diverticuli. Bl. uric acid, Cholesterol, Cal. Phosphorus, Phosphatase, Plasma Prot. Prothrombin, Bilirubin—Normal. Fragility—normal. BMR+7. Gastric analysis—normal. Wass.—negative.	Fourth attempt on sternum obtained some fluid which revealed a few normoblasts.	6-28-43 Sternum—Myelofibrosis	Iron, liver extract, yeast, and transfusions were given. None effective.	Patient has remained unchanged chemically, but requires transfusions and red blood cell suspensions. Clinically comfortable Oct. 1944.

TABLE I—*Continued*

Case No.	Name, Sex, Age, Color, Occupation	Date of Admis. Hosp. No.	Chief Complaints (on first admission) and Their Duration	Physical Findings	Laboratory Findings (Essential Findings)	Marrow Puncture Aspirations (Sternal unless otherwise indicated)	Biopsy (Site and Microscopical Diagnosis)	Treatment	Results and Remarks, also Essential Autopsy Findings (See Pathology)
(6)	F. Tic. M 56 W Piano tuner	3-11-43 FH 10183	Refractory anemia and associated symptoms—2 yr. Deep bone pains in feet and ankles—4 yrs. Progressively worse. Codeine taken—1 yr. Irregular slight fever. Weakness and lassitude.	Slight pallor—undernourished. Spleen just palpable. Liver—normal size. Lymph nodes—inguinals slightly enlarged. Tenderness over tibial crests.	X-ray—Ribs, pelvis, femurs—increased density suggestive of Paget's disease. Bl. Phosphorus. Calcium and Phosphatase. Bilirubin—normal. Prothrombin 70%. Wass., EKG, Urinalysis—neg. BMR +9. Oscillometric tests (with histamine)—normal. MCV—82. Hematocrit 24. Bleeding Time—slightly increased.	Three attempts to obtain marrow fluid from sternum were unsuccessful.	4-7-43 Sternum—Myelofibrosis. (See figure 2.)	Testosterone—25 mg. daily. i.m. from 4-9-43 to 4-30-43, and then 2×weekly until 6-3-43. Red blood cell suspensions also.	By 7-7-43 patient had no leg pains, stopped use of codeine, and returned to work. 12-17-43 patient killed by bus. (See discussion.) A piece of calvarium was secured and "although there was some replacement of the marrow by fibrous tissue" it had nearly a normal amount of hemopoietic elements. (See figure 2.)
II. Secondary									
a. Leukemia (7)	B. Bren. M 46 W Ship Fitter	11-26-42 FH 6553 1-5-43 FH 7835 6-10-43 GH 391 10-1-43 GH 4620	Refractory anemia—2 yrs. Bone pains in thighs, knees and lower back—2 yrs. Slight irregular fever, and occasional chills. Weakness. Sharp pain occasionally in upper left quad. (splenic infarct) for 6 mos.	Spleen extends 10 cm. below left costal margin. Liver—1 cm. No lymphadenopathy. Pallor.	(Elsewhere in October 1939) X-ray of pelvis—appr. normal. W.B.C. 14–15,000. Sternal puncture—normal. Spinal fluid—88 mg. protein. Urine—casts and albumin. (Lab. Findings—Jefferson Hospital) X-ray of bones—incr. density of all except skull. Blood calcium phos., phosphatase, urea nitrogen, bilirubin, Wass., sugar—normal. Urea clearance—50%. Spinal fluid—84 mg. protein. Prothrombin—30%. MCV—77; Hematocrit—27. Splenic puncture—extramedullary hematopoiesis. (See figure 1, D.) Testes enlarged—leukemic infiltration(?). Urinalysis neg. until last 6 mo. of life. Then persistent albuminuria and urea clearance of 25%.	Marrow fluid obtained by sternal puncture revealed hypoplasia of all elements.	12-9-42 Sternum—Myelofibrosis. (See figure 1.)	Because the spleen and liver had enlarged so markedly and had so adequately compensated for marrow replacement, testosterone was not started until 10-19-43. He received 25 mg. daily until death 11-6-43. The prothrombin remained consistently below normal throughout in spite of vitamin K administration. The patient received 100 r of x-ray on 11-4-43 and 11-5-43 preceding his sudden death on 11-6-43, in an attempt to control the progress of a boil (*Staph. aureus*) on his forehead.	Died 11-6-43. Myelofibrosis secondary to myeloid leukemia. Marked extramedullary hemopoiesis in liver, spleen, lymph nodes and kidneys associated with leukemic infiltrations. The foci contained megakaryocytes in abnormal preponderance.
b. Hodgkin's disease (8)	L. Dun. F 48 W Housewife	9-23-43 GH 4312 Third Admis.	Weakness, loss of weight, fever, generalized lymphadenopathy, aching bone pains (thighs and back). Abdominal soreness. Duration of symptoms—four years.	Pallor. Generalized lymphadenopathy. Liver and spleen both 10 cm. below costal margin.	X-ray—pelvis and femurs—negative. Persistent albuminuria. Severe anemia, usually a leukopenia associated with occasional normoblasts and myelocytes. Liver function tests normal.	Hypoplasia of all marrow elements.	3 lymph node biopsies. 1st. admis. (1940) Hodgkin's 2nd admis (1941) Lymphosarcoma 3rd admis. (1943) Hodgkin's	X-ray therapy—Patient had received 2000 r units of x-ray during 2 years preceding death. Transfusions.	Died 12-12-43. Autopsy findings: Reticulum cell sarcoma involving lymph nodes, spleen, liver, and bone marrow—associated with myelofibrosis. Similar case described in reference no. 26.

TABLE I—*Continued*

Case No.	Name, Sex, Age, Color, Occupation	Date of Admis. Hosp. No.	Chief Complaints (on first admission) and Their Duration	Physical Findings	Laboratory Findings (Essential Findings)	Marrow Puncture Aspirations (Sternal unless otherwise indicated)	Biopsy (Site and Microscopical Diagnosis)	Treatment	Results and Remarks, also Essential Autopsy Findings (See Pathology)
c. Carcinoma of the stomach (9)	E. Kin. M 31 W Aniline dye finisher	4-26-40 CH 10265	Epigastric pains—15 years. Nausea and vomiting, weakness. Weight loss (20 lb.) 1 mo. Dark stools.	Pallor. Jaundice. Rt. rectus scar—gastroenterostomy 1937. Spleen and liver 2-3 cm. below costal margin.	Gastroscopic exam.—malignant lesion found. Blood in stools. Prothrombin consistently low. No x-ray exam. of osseous system.	Hypoplasia of all marrow elements.		Patient received over 10,000 c.c. of blood.	Died 5-15-40. Adeno-carcinoma of stomach. Myelofibrosis—secondary to osseous metastases. Similar case described in reference No. 58. (See figure 3.)
d. Carcinoma of the prostate (10)	A. But. M 50 B Laborer in coal yard. Worked 1 year in lead plant	7-3-43 GH1308	Backache—5 wks. Chills—1 mo. Wt. loss (35 lb.)—2 mo. Occasional blood in urine—1 year.	Edema of eyelids. Uremic odor in breath. Liver—5 cm. below costal margin.	X-ray—increased density of vertebrae and pelvis suggestive of Paget's disease or metastatic lesions. Skull-negative. B.U.N. 70-130. Cal.—9.0. Phos.—4.4. Phosphatase—3.2. Wass.—negative.		Trans-urethral resection made elsewhere—Prostatic carcinoma	Patient received 4 transfusions.	Died 8-20-43. Carcinoma of prostate. Myelofibrosis—secondary to metastases of prostatic carcinoma. (Ebonized bone.) Purulent cystitis and pyelo-nephritis. (See figure 3.)
Same (11)	H. Chu. M 77 W Traveling salesman	5-9-41 DH 11950	Chills and fever—8 weeks. Loss of weight—15 lbs. in 8 weeks.	Slightly enlarged spleen. Enlarged left kidney. Auricular fibrillation. Enlarged, hard prostate.	X-ray—increased density of vertebrae and pelvis characteristic of Paget's disease. No skull x-ray made. N.P.N.—44. Albuminuria, RBC, WBC in urine. Wass.—negative.			Transfusions.	Died 5-12-41. Adeno-carcinoma of prostate. Myelofibrosis—secondary to metastases of prostatic carcinoma. Occlusion of left ureter by renal calculus, associated with pyelonephritis and intercapillary glomerulosclerosis.
Same (12)	A. Zit. M 60 W Gardener	4-24-41 DH 11388	Generalized aches in bones—2 mo. Mainly backache. Chills—4 mo.	Very obese. Dehydrated. Râles in bases of both lungs.	X-ray—increased irregular density in lumbar and lower thoracic vertebrae suggestive of Paget's disease. No skull x-ray. N.P.N.—80. Albuminuria. Wass.—neg.			Transfusions.	Died 5-6-41. Carcinoma of prostate. Myelofibrosis—secondary to metastases of prostatic carcinoma. Focal osteomyelitis of ribs. Bronchopneumonia.
s. Fibrosarcoma of marrow (13)	C. Smi. M 10 W School-boy	8-21-36 Elsewhere	Bone pain in neck—1 year. Bone pain in legs—3 mo. Swelling of knees, ankles, elbows, fingers—2 months. Pallor and nosebleeds—2 mo.	Pallor. Appeared chronically ill. Spleen, liver and nodes—normal. Atrophy of most muscles.	X-ray—evidence of both an osteolytic and osteoplastic process in vertebrae and long bones, associated with periostitis. Skull—neg. Wass., NPN, Cholesterol, Calcium, Phosphorus, BMR, Urine, Bence-Jones Proteinemia, Undulant Fever Agglutination, etc.—negative or normal. MCV—47; Hematocrit—19.	Hypoplasia of all marrow elements.	Sternum—Myelofibrosarcoma	Transfusions.	Died 1-11-37. Myelofibrosarcoma of vertebrae, ribs, sternum and femur. Multiple tiny metastases in kidney. Liver, thyroid, lungs, heart, lymph nodes—negative. Similiar case described in reference No. 71. (See figure 3.)

The first cases of myelofibrosis were described by Heuch [43] of Heidelberg, Germany, in 1879. In the United States the first case was described by Donhauser [44] of Philadelphia in 1908; later other cases were presented by Ballin and Morse [45] in 1927 and by Chapman [46] and Stephens and Bredeck [47] in 1933. There are probably less than 200 cases described in the world's literature.

Clinically, idiopathic primary generalized myelofibrosis is usually characterized by slowly progressive weakness, splenomegaly, bone pains and refractory anemia [11] (table 1). The latter is usually associated with thrombocytopenia, leukopenia and the presence of a small percentage of immature (or primitive) red and white blood cells in the peripheral blood stream (table 2). From an anatomico-pathological standpoint such peripheral blood findings are given the term "myelophthisic anemia" (first used apparently at the beginning of the century by Pappenheim to indicate a wasting or weakness of the bone marrow [48]), but from a clinico-pathological standpoint the term "leuko-erythroblastic anemia" has been used by Vaughn [49] since 1934 to indicate "any widespread invasion of red marrow by tumor, proliferating leukocytes, fibrosis or bony tissue." [50, 21] Since then many authors [10, 11, 16, 18] have pointed out that myelofibrosis may be primary or secondary to encroachment upon the marrow cavity by cells, either cancerous, metabolic (Gaucher's disease, etc.), fibroblastic or bone (cortical bone cells as in osteopetrosis, or endosteal bone cells as in myelosclerosis). *Roentgenologically,* there may or may not be osteoplastic or osteolytic changes [11] which are dependent upon the extent of the myelofibrosis or associated myelosclerosis. *Pathologically,* in some cases it may be difficult to determine whether myelofibrosis or myelosclerosis is the initial process. However, fundamentally it is the marrow changes that cause the anemia and ultimate death of the patient and not the bone changes per se. Of course the amount of compensatory extramedullary hematopoietic enlargement of the spleen, liver and lymph nodes usually depends upon the amount of red marrow replaced by fibrosis. The fatty marrow of the extremities usually remains fatty. In a few cases [51, 52, 53, 54, 55] myelofibrosis has been described in association with gelatinous or fatty changes of the marrow. (Such features may depend upon the time element as brought out experimentally by the ligation of the nutrient vessel of a femur of a rabbit.[8] Four to 14 days after ligation, the marrow becomes necrotic, later gelatinous.) A positive *diagnosis* of myelofibrosis can only be made after microscopic examination of a biopsied specimen of marrow (preferably from sites of red marrow, as sternum, rib, etc.), although failure to aspirate marrow fluid through a sternal puncture needle should make the clinician suspicious of the disease.[11, 16, 20, 47] In the *treatment* of generalized primary myelofibrosis obviously radiotherapy and splenectomy are contraindicated,[11, 12, 18, 26, 53, 57] and transfusions are but palliative.

B. Clinically, generalized myelofibrosis secondary to the various diseases

TABLE II

Findings in Peripheral Blood of Cases with Primary or Secondary Myelofibrosis

	Name, No. and Date	Hgb %	R.B.C. in Millions	W.B.C. in Thousands	Plate. in Thousands	Normoblasts (per 100 W.B.C.)	Poly. %	Myelocytes %	Myeloblasts %	Eos. %	Baso. %	Lymph. %	Mono. %
A. Focal													
I. Primary	1. P. Sil.												
	5-28-39	82	3.9	8.7			65			2		20	13
	3-28-42	78	4.5	11.6			63			3		33	1
II. Secondary	No cases presented												
B. Generalized													
I. Primary	2. P. Hob.												
	11-10-43	41	1.9	2.5	28	2	22	1				70	5
	12-8-43 *£	83	4.4	2.2	42	1	24					62	14
	1-4-44 £!	51	2.8	2.9	10	2	42	2				36	20
	3. E. Lac.												
	7-12-43	21	1.7	4.9	12	1	44	3			1	44	8
	8-16-43 *	39	2.4	4.7	76	1	37	1		1		58	3
	9-18-43 *	46	2.2	4.5	52	2	41					57	2
	12-15-43	24	1.6	6.0			29	2		1		63	5
	1-21-44 !	26	1.6	6.3	40	8	30	1		1		57	2
	4. J. Lam.												
	1-13-44	25	1.5	5.0		7	34	14	5	1	4	26	16
	1-25-44 *£!	52	2.6	4.1	40	2	40	14	1		6	27	12
	5. R. Mar.												
	6-9-43	54	2.3	1.6		6	60			2		31	7
	6-15-43 *	50	2.4	1.9	156	3	63	1	1			30	5
	10-8-43 *£	60	2.6	2.8			52					41	7
	1-24-44 *£	44	2.8	2.3			52					35	13
	6. F. Tic.												
	3-15-43	49	2.5	2.9	76	2	65		2	1		30	2
	4-16-43 *!	51	2.7	2.4	12	2	37	12	9		1	21	10
	5-26-43 !	47	2.5	4.4	56	12	60	11	6			19	4
	8-14-43 !	61	3.6	6.0			74					22	4
II. Secondary													
a. Leukemia	7. B. Bren.												
	11-28-42	55	3.5	15.8	600	2	41	24	2		1	21	13
	1-8-43 *	47	2.8	13.0	814	4	46	19	8		6	18	3
	6-3-43 *	43	2.4	14.4	800	8	45	20	9		12	8	6
	8-19-43 *£	44	2.2	20.4	1,150	4	32	29	13	1	8	14	13
	11-5-43 *£!	68	3.8	12.1	424	1	42	17	22	6	2	9	1
b. Hodgkin's disease	8. L. Dun.												
	9-24-43	39	2.8	10.0			78			3	1	12	6
	10-26-43 *£	63	4.0	10.2	60	3	81	1		2	1	7	5
	12-9-43 *£	74	3.9	1.3			71					13	16
c. Carcinoma of the stomach	9. E. Kin.												
	5-6-40	28	1.3	9.1	248	7	67	4		1		28	
	5-9-40 *	20	1.0	8.6	204	11	61	11		2		26	
d. Carcinoma of the prostate	10. A. But.												
	8-26-42	45	2.3	7.0		1	74	1		6		12	6
	7-3-43	42	2.4	8.2		8	75	1		1	1	22	1
	11. H. Chu.												
	5-10-41	55	2.9	20.0			85	2				11	2
	12. A. Zit.												
	5-2-41	52	3.2	6.2		5	75	2		1		15	2
e. Fibrosarcoma of bone marrow	13. C. Sml.												
	10-15-36	60	4.0	7.1	70	2	46	11	6	1		32	4
	11-17-36 *	42	2.4	2.2	60	4	42	6	4	2		44	2

* After administrations of transfusions.
£ After administrations of red blood cell suspensions.
! After administrations of testosterone.
Red blood cell suspensions consist of 250 c.c. of packed red blood cells, and 250 c.c. of equal amounts of isotonic saline and isotonic glucose.

mentioned above in the introduction is characterized, of course, by the disease processes responsible for or associated with the fibrosis of the marrow. In table 1 there are listed cases of myelofibrosis secondary to Hodgkin's disease and to neoplasms of the stomach, prostate and bone marrow. The refractory type of anemia, myelophthisic or leuko-erythroblastic, is noted in these cases as in those with primary myelofibrosis. *Roentgenographic* evidence of osteolytic or osteoplastic changes may or may not be present; and the radiologic changes may appear late in the course of the disease.[58] *Pathologically*, fibrosis of the marrow (biopsy) and extramedullary hematopoiesis (enlarged spleen and liver) can be noted. The extent of the latter usually depends upon the amount of marrow that has been replaced by the original process and the secondary myelofibrosis or myelosclerosis. The *treatment* depends upon the process which causes or is associated with the fibrosis of the marrow, or upon the symptoms produced. In cancer of the breast or prostate, etc., with osseous metastases which cause bone pain, roentgen-radiation is indicated.[58, 59] Other symptomatic treatment is but palliative.

C. Pathology. A discussion of the changes observed in the biopsy and autopsy specimens of these cases of generalized myelofibrosis, both primary and secondary, follows, and the essential pathological findings in each case are listed in the accompanying tables (table 3 A and table 3 B). Since the lesions are fundamentally the same in all cases, a distinction between the primary (or idiopathic) and secondary forms of generalized myelofibrosis is not necessary. The changes may be conveniently considered from the following aspects: (1) endosteal bone, (2) bone marrow, and (3) extramedullary hematopoiesis.

(*1*) *Bone changes.* There may be a diffuse or focal proliferation of endosteal bone. Osteoblasts are usually present. Sometimes they are very large, active and surround almost every spicule of bone, whereas at other times they are greatly attenuated and sparse. Occasionally there are definite underlying zones of light pink staining osteoid tissue which are either sharply demarcated from the subjacent bone or merge gradually with it. Usually, however, the osteoid tissue is minimal or absent and spicules are composed entirely of osseous tissue. These are many times the normal thickness, deep pink staining and most often sclerotic. The lacunae ordinarily are less numerous than normal and the bone is either irregularly lamellated or shows no lamellation whatever. When lamellae are still discernible the separating bluish stained fibrils when present are very ill defined, hazy in appearance, and usually short. Neither do they have the concentric appearance ordinarily seen, nor are they distinct enough to be confused with the mosaic structure so constantly observed in osteitis deformans. There is always a conspicuous paucity, or a complete absence of osteoclasts. Those that are found, however, are of the ordinary multinucleated variety.

(*2*) *Changes in the marrow* may occur either separately or in association with myelosclerosis. Some cases apparently start as a diffuse or focal hypo-

plasia of all the marrow elements. There then appears a gradual increase in the underlying reticulum, first as a fine fibrillary and even somewhat myxomatous connective tissue, but later there is a gradual increase of collagen until the entire structure becomes densely fibrotic. The cellularity of the fibrous tissue varies. Sometimes the nuclei are very large, swollen and numerous and seem to blend intimately with the adjoining osteoblasts, whereas at other times they are small and sparse. Early in the process the vessels are fairly numerous and thin walled. Later they are inconspicuous. Scattered between the fibrous tissue strands there are present

TABLE IIIA

Bone Changes in Biopsied and Autopsied Specimens

	Case No. and Name	Bones Examined	Myelosclerosis	Myelofibrosis	Remaining Hematopoiesis	Megakaryocytes	Tumor Metastases
A. Focal							
I. Primary	1. P. S.	Tibia (Biop.)	Severe	Moderate	Very occasional foci	None	None
II. Secondary	No cases presented						
B. Generalized							
I. Primary	2. P. H.	Stern. (Biop.)	Extensive	Diffuse; Early	None	Normal	None
	3. E. L.	Stern. (Biop.)	Moderate	Diffuse; Early	Focal; Hyperplastic	Normal	None
	4. J. L.	Stern. (Biop.)	Moderate	Moderate	Focal; Hyperplastic	Increased	None
	5. R. M.	Stern. (Biop.)	Extensive	Diffuse; Early	Focal	Normal	None
	6. F. T.	Stern. (Biop.)	Extensive	Diffuse; Severe	Focal; Hyperplastic	Greatly increased	None
		Skull (Autop.)	Severe	Slight	Almost normal	None	None
II. Secondary							
a. Leukemia	7. B. B.	Stern (Biop.)	Severe	Diffuse; Extensive	Focal; Hyperplastic	Greatly increased	None
		Ribs, Stern., L. Vert. (Autop.)	Severe	Diffuse; Extensive	Focal; Hyperplastic	Greatly increased	None
b. Hodgkin's disease	8. L. D.	Ribs, Stern., D. and L. Vert. (Autop.)	None	Diffuse; Very early	Diffuse; Hypoplastic	Normal	Large necrotic masses of Hodgkin's tissue
c. Carcinoma of the stomach	9. E. K.	D. and L. Vert. (Autop.)	None	Diffuse; Early and late	Consid. necrosis; Very occ. foci; Hyperplastic	Normal	Only few cells from carcinoma of the stomach
d. Carcinoma of prostate	10. A. B.	Skull, Stern., Ribs, D. and L. Vert. (Autop.)	Severe	Focal areas of extensive fibrosis	None recognized	None	Diffuse from carcinoma of the prostate
"	11. H. C.	D. and L. Vert. (Autop.)	Extensive	Diffuse; Early and late	Islands of normal	Normal	None, but patient had carcinoma of prostate
"	12. A. Z.	Ribs, L. Vert. (Autop.)	Ribs—Slight Vert.—None	Diffuse; Early and late	Few scattered foci	Normal	Few cells from carcinoma of the prostate
e. Fibrosarcoma of bone marrow	13. C. S.	Stern. (Biop.)	Moderate	Diffuse	Focal but often necrotic	Decreased	Sheets of myelofibrosarcoma cells
		Ribs, Stern., Vert. (Autop.)	Moderate	Diffuse	Focal but often necrotic	Decreased	

foci of regular or greatly hyperplastic hematopoiesis which usually contain both myelogenous and erythrocytic cells. Although megakaryocytes ordinarily are not increased sometimes they may be so numerous as to overshadow all other elements. In some cases there is apparently no preliminary hypoplasia of the marrow, but instead focal necrosis of the blood forming elements with varying amounts of hemorrhagic extravasation. Although these regressive changes most frequently occur at the site of metastatic tumors, the latter do not necessarily evoke such a reaction, for occasionally there are only a few nests of metastatic tumor cells, no necrosis, and a dif-

TABLE IIIB

Extramedullary Hemopoiesis in Autopsied Specimens

	Case No. and Name	Spleen	Liver	Lymph Nodes	Lungs	Kidney
B. Generalized II. Secondary *a.* Leukemia	7. B. B.	Wt. 2,650 gm. Diffuse hematopoiesis. Numerous megakaryocytes	Wt. 4,840 gm. Diffuse hematopoiesis. Numerous megakaryocytes	Diffuse hematopoiesis. Numerous megakaryocytes	Focal hematopoiesis with scattered megakaryocytes	Focal hematopoiesis. Numerous megakaryocytes
b. Hodgkin's disease	8. L. D.	Wt. 550 gm. No hematopoiesis. Hemosiderosis	Wt. 1,860 gm. No hematopoiesis. Hemosiderosis	None	None	None
c. Carcinoma of the stomach	9. E. K.	Wt. 670 gm. Diffuse hematopoiesis	Wt. 2,950 gm. Diffuse hematopoiesis	None	None	None
d. Carcinoma of the prostate	10. A. B.	Wt. 40 gm. No hematopoiesis. Hemosiderosis	Wt. 1,630 gm. No hematopoiesis.	None	None	None
"	11. H. C.	Wt. 350 gm. None	Wt. 1,810. None	None	None	None
"	12. A. Z.	Wt. 320 gm. Focal hematopoiesis. Few megakaryocytes	Wt. 2,310 gm. Diffuse hematopoiesis. Few megakaryocytes	None	None	None
e. Fibrosarcoma of bone marrow	13. C. S.	Wt. 70 gm. Focal hematopoiesis	Normal size for age of patient; focal hematopoiesis	None	None	None

fuse fibrosis which is out of all proportion to the amount of tumor tissue present.

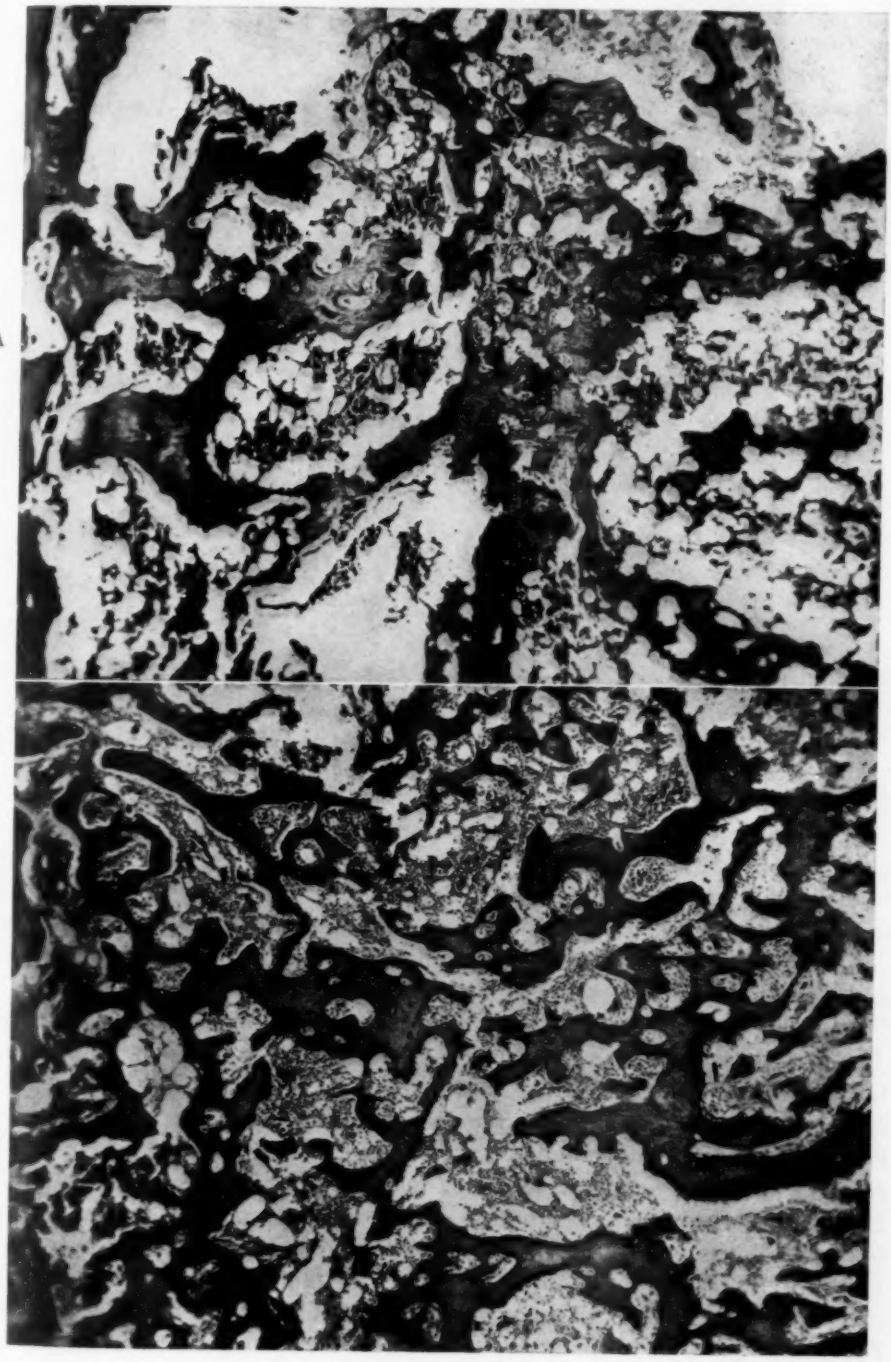
(*3*) *The development* of *extramedullary hematopoiesis* appears to be a compensatory mechanism and entirely dependent upon the degree of myelosclerosis and myelofibrosis. In this series of seven autopsied cases there were four (nos. 7, 9, 10 and 12) in which such changes in the marrow were far advanced. In three (nos. 7, 9 and 12) of these there was unequivocal extramedullary hematopoiesis. The organs most frequently involved are the liver and spleen, but hematopoiesis may also be seen in the lymph nodes, lungs and kidneys. Grossly, the liver and spleen are almost always enlarged, and occasionally they assume huge proportions. They are invariably firmer than normal. Microscopically, foci of myelocytic and erythrocytic cells are found scattered throughout the organs. Ordinarily megakaryocytes

are in abeyance, but at times they may be so increased as to overshadow all other constituents, as in case 7.

Discussion

A. Etiology. The etiology of myelofibrosis is poorly understood, but the experimental approaches to this subject are most promising. As can be observed in the above classification (*B* II 14,) many substances can be responsible for the development of fibrosis of the bone marrow. One could assume, therefore, that myelofibrosis has many and varied causes and consequently many and varied treatments. It has been demonstrated that estrogens can be a cause of fibrosis of the bone marrow.[33] Since testosterone acts as an inhibitor to estrogens, testosterone can inhibit the myelofibrosis caused by excessive estrogens [35]; or if the preponderance of estrogens in a case of myelofibrosis were due to an inability of the liver to conjugate the estrogens, in normal quantities, one might give the vitamin B complex which would theoretically enhance the conjugating ability of the liver [56] and thereby overcome the progressive course of myelofibrosis. Estrogens, however, may function in a variety of ways, for in some 40 cases of prostatic carcinoma Huggins [60] has shown that following estrogen therapy, "in four patients extensive osseous metastases have completely disappeared to radiographic examination." (Whether these four cases had myelofibrosis secondary to the osseous metastases is unknown, because biopsies were not made.) This type of regression is possibly similar to that seen when Paget's disease reaches the healing stages. Jaffe [61] noted that in the healing process of Paget's disease there is a "tendency to the return of a normal appearance of both the bone and bone marrow" and "the fibrous marrow becomes replaced by more lymphoid and fatty marrow." The *mechanism* for the formation of *secondary myelofibrosis,* in patients with cancerous processes with osseous metastases and in those with Paget's disease, is probably the associated chronic occlusion of the blood vessels of the marrow (chronic infarction can be produced experimentally by the injections of carbon particles [9]). It is known that acute occlusion of the blood vessels to the marrow, as in caisson disease [62] (gas bubbles), will not cause myelofibrosis. Therefore, in the treatment of secondary myelofibrosis, one of the objectives is to inhibit or overcome chronic occlusion of the blood vessels of the marrow; another is to overcome endocrine imbalances.

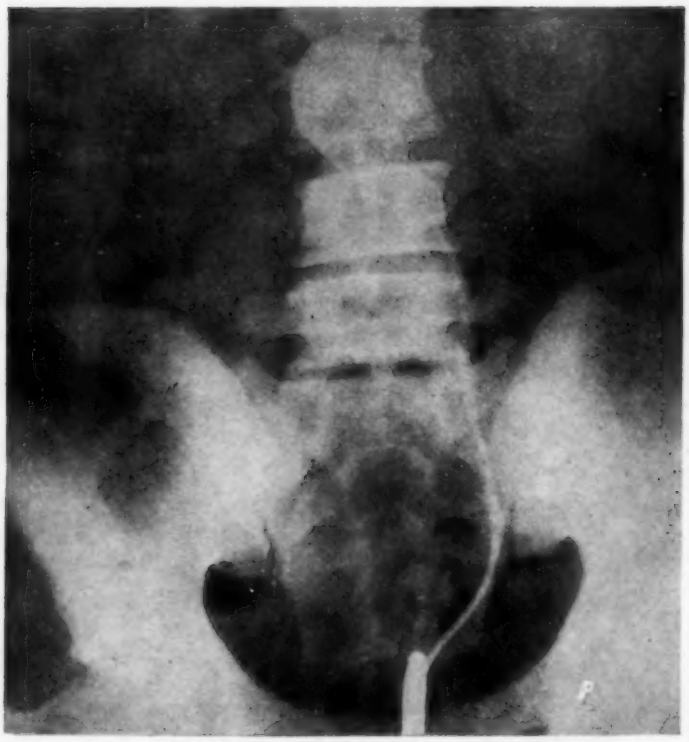
Martland [30] has brought out one interesting feature—that irradiations of radium, thorium, and possibly other elements made radioactive artificially, administered internally, when in direct contact with bone marrow cells for long periods of time ("the third stage") ultimately cause myelofibrosis, but that irradiations of roentgenographic machines or of radium applied externally (to the skin) cause aplasia or hypoplasia of the marrow. One would expect, therefore, that the former type of irradiation is more apt to cause narrowing of the blood vessels of the marrow than the latter.



A

B

FIG. 1. (*Continued on page 876.*)



C

FIG. 1. (*Continued on page 877.*)

Curiously enough, such an apparently abstract factor as temperature plays a part in the functioning of bone marrow. Huggins et al.[63] showed by surgically inserting the tip of the intact tail of a rat into its own abdomen that the increased heat of the abdomen made the marrow within the tip red and active whereas the marrow within the remainder of the tail was fatty and hematopoietically inactive. One of us (L. A. E.) inserted aspirated red femoral marrow fluid of rabbits into the anterior chambers of their own eyes. The marrow quickly became yellow. Within a month (upon aspiration of the anterior chamber) the predominating cells were red cells and lymphocytes; and within two months the marrow had been replaced by bone and fibrous tissue. Lowered temperatures could have been responsible for the results. The low temperature of the marrow of the extremities may be the explanation of the clinical finding, apparently first pointed out by Piney[15] that metastases occur in red marrow and rarely, if ever, in fatty marrow (where temperatures are low). Whereas the blood producing ability of the marrow probably depends upon temperature, fibrosis of marrow does not. Fatty marrow and fibrous marrow are two entirely different conditions.

Bunting[36] and later Nettleship[38] produced myelofibrosis in rabbits by first injecting ether soluble extracts of rabbit marrow into guinea pigs and

D

E

FIG. 1. Case 7. *A*. Biopsy of sternum—showing fibrosis of marrow and myelosclerosis. *B*. Sternum (autopsy)—showing fibrosis of marrow and myelosclerosis. *C*. Roentgenogram of pelvis—showing generalized increased density of bones, also density of bones compared with density of cystoscope. *D*. Splenic puncture—showing extramedullary hematopoiesis, normoblasts, myelocytes, megakaryocytes, etc. *E*. Liver (autopsy)—showing extramedullary hematopoiesis (normoblasts, myelocytes, megakaryocytes, etc.).

then later injecting guinea pig sera which contained the marrow antibodies into other rabbits. Miller and Turner [42] have produced myelofibrosis in guinea pigs by the injections of an ether soluble extract of urine of patients suffering with myeloid leukemia (figure 3 D). From an embryological standpoint one might say that the three primitive layers, ectoderm, endoderm and mesoderm, have progeny which after various differentiations reach certain destinies. The first two layers ultimately are desquamated, the first exteriorly, the second internally, and the progeny of mesoderm which includes bone marrow and bone becomes fibrous tissue. Bone marrow cells or white blood cells when grown in culture tubes lose their differentiations and become fibroblastic. Miller and Turner [42] have demonstrated that if bone marrow cells are given the proper organizers or stimulants the normal marrow cells become either myeloid or lymphoid in character depending upon the amount of myeloid-stimulating and lymphoid-stimulating substances [64] present. By giving both of these substances in large quantities to guinea pigs, they have produced Hodgkin's-like tissue in the bone marrow. This tissue has much fibrosis and many megakaryocytic-appearing cells. Firket et al.,[37] by the injection of saponin, have also produced infiltrations of megakaryocytes in the liver, spleen, lymph nodes, etc., of rabbits and if the injections were continued over a long period of time fibrosis of marrow appeared. Therefore, it can be seen that one can experimentally produce fibrosis and megakaryocytosis of the bone marrow, a condition which has been found in man (case 7, table 1).

In summary, one can observe that many factors, such as occlusion of the blood vessels of the bone marrow, infarction of the marrow, temperature, hormones, organizers, etc., can play parts in the etiology of myelofibrosis.

B. Treatment (tables 1 and 4). As brought out under etiology it is possible that some cases of primary myelofibrosis may be due to excessive estrogens. Acting upon that assumption and upon the experimental work of Miller et al.,[35] four cases (nos. 2, 3, 4 and 6) of primary myelofibrosis and one of secondary myelofibrosis (no. 7) were given testosterone in spite of the fact that the excreted urinary hormone values (table 4 and ref. no. 67) in three of these could not be considered particularly abnormal. In the fourth, a male (no. 4, table 4), a low androgen level and a high estrogen level were noted. The use of testosterone was first brought out in a previous paper.[11] After testosterone was given to three of these patients (nos. 2, 4 and 6) no significant changes were noted in the urinary hormonal assays.

Case 6 responded best to the administration of testosterone. In fact, the patient had a partial remission, i.e., the anemia and leukopenia became less severe, the bone pains disappeared within two months after the initial treatment, and he returned to his work. (The remission may have been spontaneous.) The treatment was then stopped and patient remained in the remission until struck in the head by a bus and killed seven months after initial treatment. The accident occurred in another state and unfortunately

the coroner was content with an examination of the head alone to prove that cerebral hemorrhage was present. The marrow of the calvarium (figure 2 B), the only specimen obtained at autopsy, can be considered as being near normal in hematopoietic elements, although some fibrosis is present, as is true in normal individuals. In this case, as in most of the others that follow, the roentgenographic findings indicated that all the bones of the skeleton were abnormally dense.

Case 3 was given testosterone intramuscularly and yeast orally. There was an immediate rise in the reticulocyte level to 7 per cent, an increase in

TABLE IV

Urinary Hormone Assays in Cases of Primary or Secondary Generalized Myelofibrosis

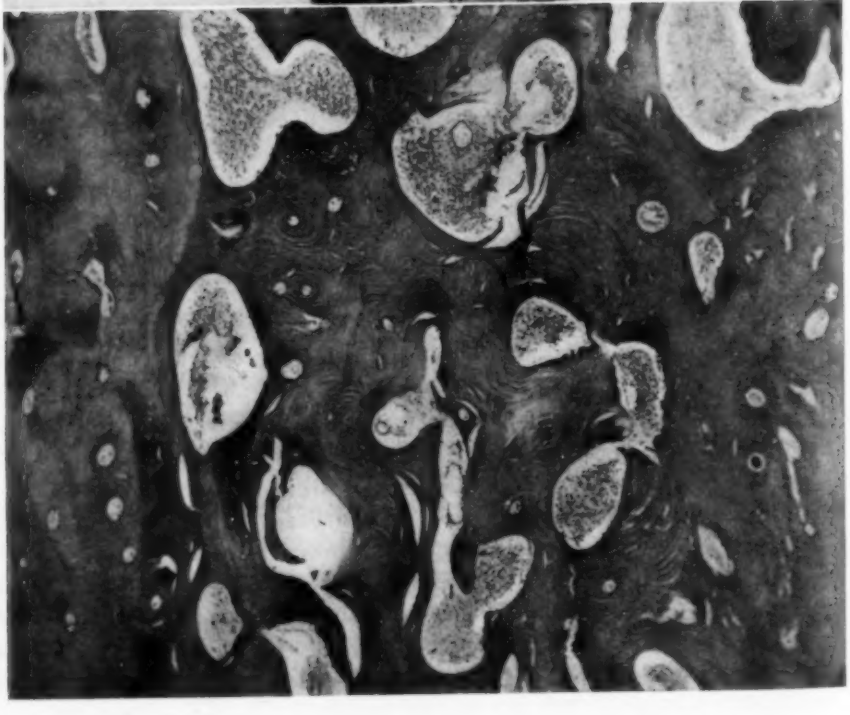
	Name, No. and Date	Estrogens Free—Combined (Mouse units/24 hrs.)		17 Ketosteroids (mg. equiv. of andosterone/24 hrs.)	Androgens (International units/24 hrs.)	Gonadotropin (International units/24 hrs.)	Remarks
		Free	*Comb.*				
	Normal (See Ref. No. 67)						
	Men (average)		10	15	75	10	
	Women (average)		10	10	50	(Variable during menses)	
A. Focal							
I. Primary	No studies made						
II. Secondary	No studies made						
B. Generalized							
I. Primary	2. P. H.						
	12-10-43	6—*	6—	5.5	11		Before testosterone
	1-10-44	6—	6	24.0			After testosterone
	4. J. L.						
	1-20-44		30	4.5			Before testosterone
	2-7-44	6	22	5.5		Non-demonstrable	After testosterone
	5. R. M.						
	6-15-43	3—	3—				
	6. F. T.						
	4-2-43	6—	6—	22.5			Before testosterone
	5-6-43		6—	7.2		Non-demonstrable	After testosterone
	7-7-43		6—		14	Non-demonstrable	After testosterone
II. Secondary							
a. Leukemia	7. B. B.						
	12-21-42		13—	6.0		Non-demonstrable	Before testosterone
	1-8-43			5.0	25		Before testosterone
	6-11-43		6—	10.7	16	Traces	Before testosterone

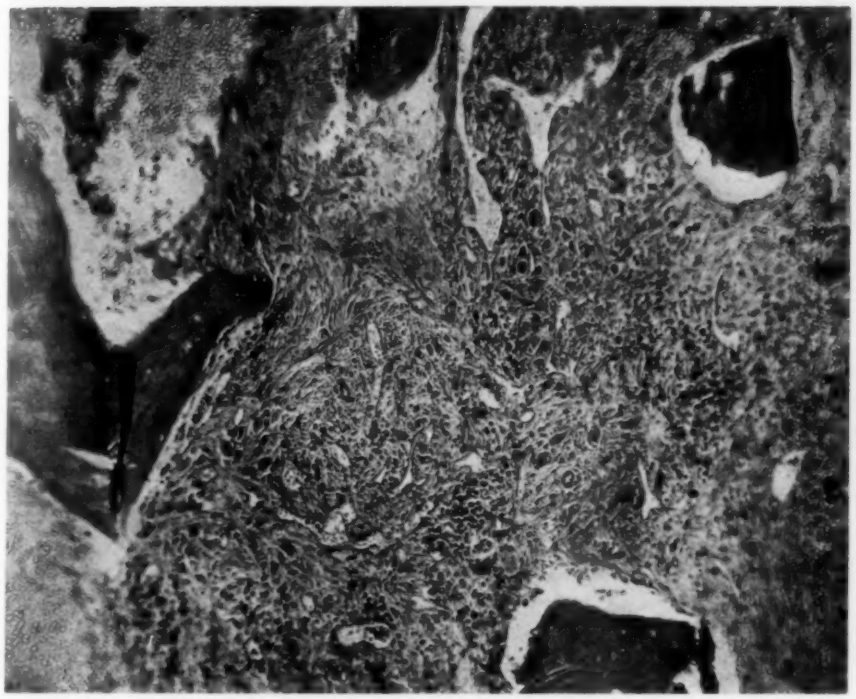
* The minus sign (—) behind these figures means: less than.

physical activity, and a rosy color appeared in her cheeks. This patient has sisters, one two years older and another two years younger, and the mother states that the patient was much taller than either of her sisters at similar age periods. This observation would compare favorably with the experimental findings reviewed by Gardner and Pfeiffer [33] that excessive amounts of estrogens cause bone to lengthen abnormally rapidly and to accelerate the formation of endosteal bone. It also conforms to the work of Silberberg and Silberberg.[40] The majority of cases of myelofibrosis seen in children occur in females. Since receiving testosterone this patient has had some vaginal discharge, but she has not gained weight. She was also given a few

A

B





C

FIG. 2. Case 6. (Primary myelofibrosis.) *A*. Biopsy of sternum—showing fibrosis of marrow. *B*. Skull (autopsy)—showing regeneration of marrow presumably occurring after administration of testosterone. Case 4. (Primary myelofibrosis.) *C*. Biopsy of sternum—showing fibrosis of marrow.

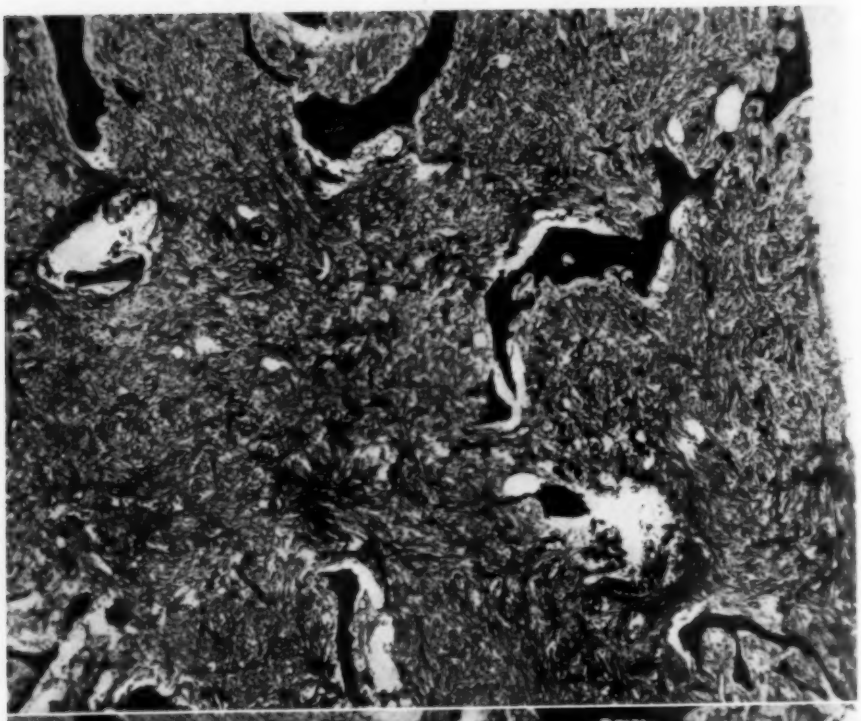
injections of adrenal cortical hormone in the hope of depressing the total number of lymphocytes in the peripheral blood stream. This patient now (Oct. 1944) is in a partial remission.

Case 2 had unusual blood findings, i.e., marked leukopenia with lymphocytosis. Testosterone apparently had no effect on the course of his disease and he died six months after the onset of his illness. A case similar to this one was described by Pinkerton.[24]

Case 4, like so many others, was considered pernicious anemia and was given intensive iron and liver therapy without response before being admitted to Jefferson Hospital. His response to testosterone is now being closely observed, because of the abnormally high urinary estrogen level (table 4). During the seven months preceding Oct. 1944 the patient has required 55 red blood cell suspensions. In this case the myelofibrotic process seems to continue to be progressive.

Case 7 was not given testosterone until late in the course of the disease. Because his spleen and liver had enlarged and hematopoietically compensated so adequately for the marrow which had been replaced by fibrous tissue it was felt not necessary to administer other than yeast and an occasional

A



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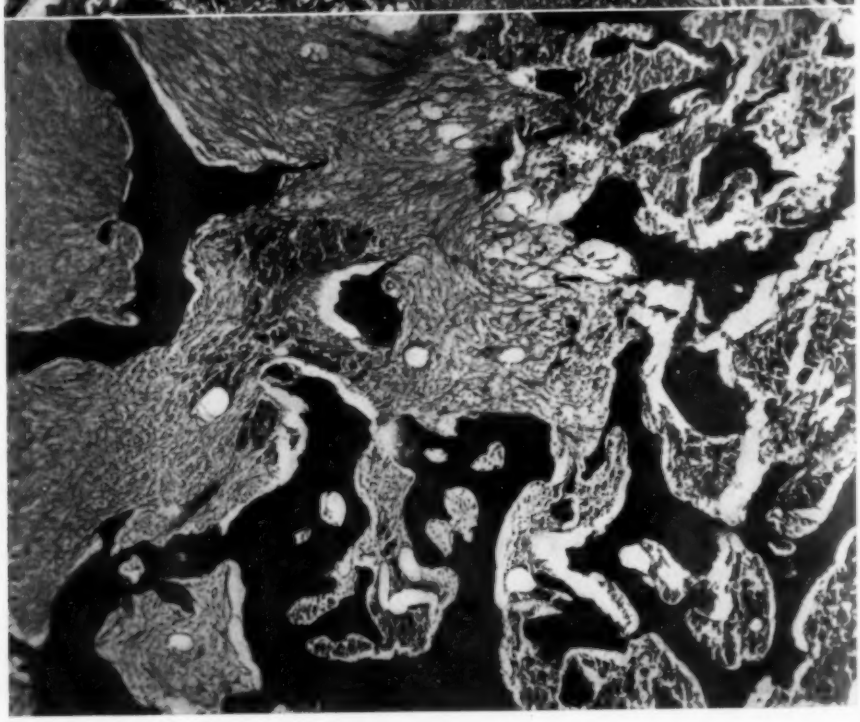

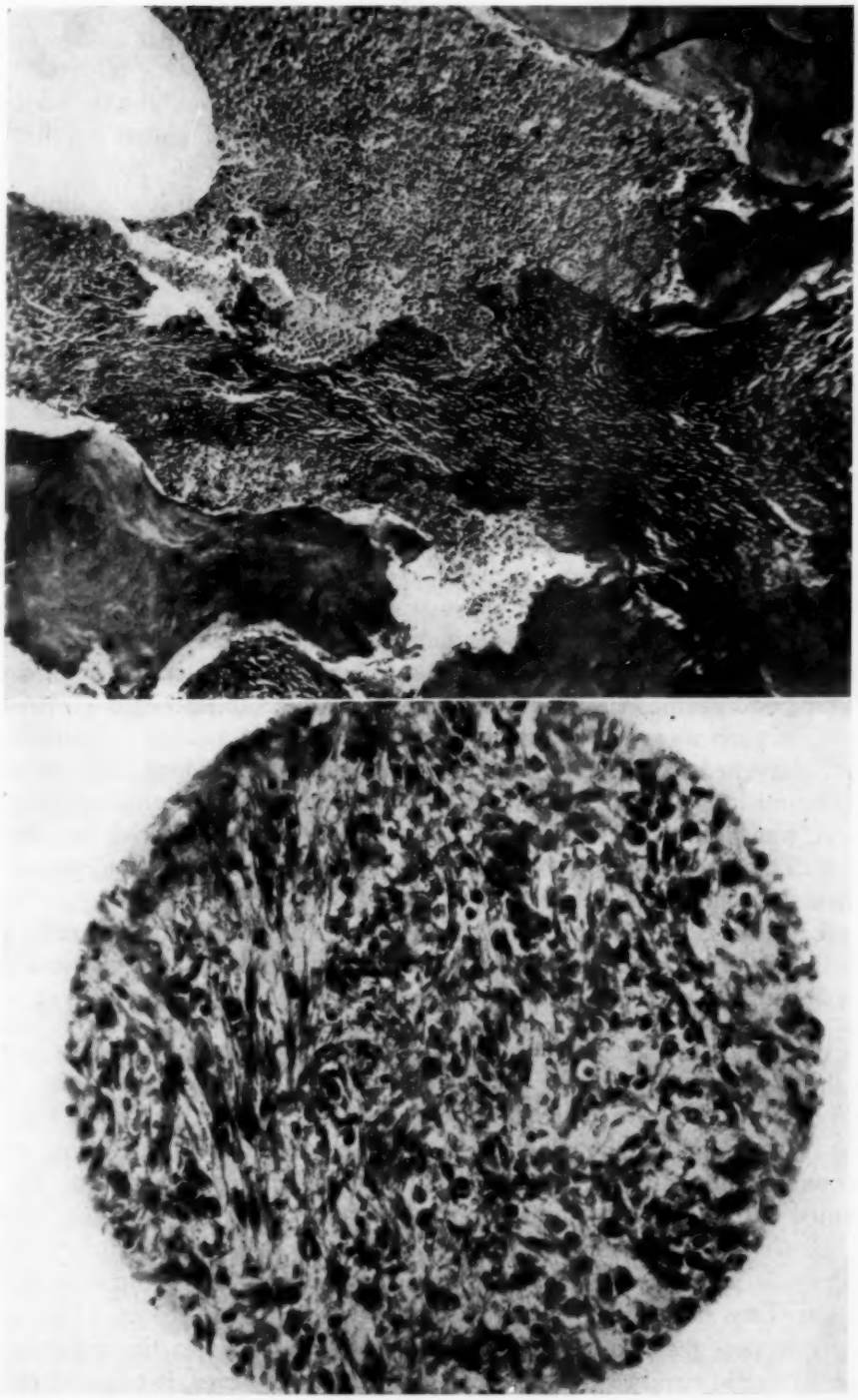

FIG. 3. *A*. Case 9. (Carcinoma of stomach with osseous metastases.) Myelofibrosis of lumbar vertebra. *B*. Case 10. (Carcinoma of prostate with osseous metastases.) Myelofibrosis of lumbar vertebra. *C*. Case 13. (Myelofibrosarcoma.) Sternal biopsy showing tumor associated with marrow necrosis and early myelofibrosis. *D*. Fibrosis of femoral marrow of guinea pig produced by injection of myeloid stimulating substance. (See discussion.)

500 c.c. suspension of red cells (he had consistently normal blood protein levels). In fact, he was not given testosterone until after a large boil developed on his forehead which could not be controlled medically or surgically and so perhaps unwisely roentgen radiation was administered. He died suddenly after the second irradiation—a total of only 200 *r*. A case similar to this one was described by Hickling.[12] Although it was difficult to decide whether this case was or was not secondary to leukemia, it probably was the latter for the following reasons.

1. Although the findings of a sternal puncture three years before death were normal, the peripheral blood findings always were characterized by a leukocytosis and thrombocytosis, both of which persisted throughout the entire course of the illness.
2. Sternal punctures performed later revealed hypoplasia of the marrow elements.
3. The sternal biopsy revealed fibrosis of marrow. Leukemic changes were not present.
4. The extramedullary hematopoietic foci obtained from the splenic puncture fluid and at autopsy were composed of not only essentially normal marrow components but also leukemic cell infiltrations.
5. The extramedullary hematopoiesis was extensive—the spleen weighed 2,650 grams, the liver weighed 4,840 grams and perhaps 20 per cent of each was made up of extramedullary hematopoiesis. Extramedullary hematopoiesis was also prominent in the kidneys, lymph nodes and lungs. The volume of active extramedullary hematopoietic foci was probably greater than the active marrow replaced by fibrosis. This probably explains the persistent leukocytosis, myelocytosis and thrombocytosis.
6. Terminally, 22 per cent of the circulating white blood cells were myeloblasts, whereas the number of white cells in the peripheral blood ranged around 20,000 per cu. mm.

It must be reëmphasized at this point that testosterone was given because of the experimental evidence presented previously and because no other medication seemed to have an equally good rationale. It was given in the hope that it would inhibit the progression of the myelofibrotic process, but not to reconvert fibrous into hematopoietically active marrow. It must also be pointed out that case 5 is quite comfortable clinically without testosterone.

C. General. Although generalized myelofibrosis, either primary or secondary, is perhaps rather rare, it is probably much more common than is indicated by the number of published reports of these cases. One could easily suppose that many of the cases of refractory or aplastic or hypoplastic anemia are in reality cases of myelofibrosis. (However, it must be emphasized that fibrosis of the bone marrow is distinctly different from aplasia of the bone marrow; extramedullary hematopoiesis rarely, if ever, occurs in

aplastic anemia.) At most autopsies few if any specimens of marrow are obtained, because of technical difficulties, such as sawing, decalcification, etc., and limited autopsy permission. If marrow of all the bones were routinely examined, myelofibrosis would probably be found to be as common as leukemia. (At this point it must be pointed out that we are discussing only those cases in which the fibrosis of the marrow has reached the pathological level, for there are those [14] who feel that fibrosis of the marrow is also a normal process and that it normally precedes ossification or bone formation.) From a clinical standpoint, if sternal biopsies were carried out in all cases of refractory anemia, more cases would undoubtedly be discovered. Also, in those cases of anemia in which repeated sternal punctures are unsuccessful, sternal biopsies should always be made.[11] The diagnosis of myelofibrosis must be considered when the evidence of myelophthisic or leuko-erythroblastic anemia is found, i.e., when immature red cells (normoblasts or erythroblasts) and white cells (myelocytes, myeloblasts, tumor cells, etc.) are present in the peripheral blood. Bunting [36] in 1906 said that the appearance of such immature red cells in the circulating blood is an expression of injury to the bone marrow and that the circulating normoblasts could originate from extramedullary hematopoietic foci. Bone marrow can be injured by various cells, i.e., bone cells (Paget's disease, myelosclerosis), tumor cells (metastatic carcinoma, myeloma, etc.), metabolic cells (xanthomatosis, Gaucher's disease, etc.), leukemic cells, etc., in addition to fibroblastic cells.

Hickling [12] pointed out in discussing myelofibrosis that "there are certain features which are more common in these cases than in typical cases of myeloid leukemia among which are abnormal bone formation in the bone marrow cavities and the presence of large numbers of giant cells in the myeloid tissues of the organs." It would seem that he implied that the endosteal thickening caused occlusion of marrow vessels (as occurs also in Paget's disease, metastatic carcinoma, etc.) which resulted in marrow fibrosis. This, of course, brings up the question—is myelosclerosis or myelofibrosis the underlying initial process? And the question cannot be answered adequately. There are cases of myelofibrosis, however, without associated myelosclerosis.[69] Schiller [65] made the following statement—"osteosclerosis (myelosclerosis) frequently is followed by myelofibrosis; primary myelofibrosis in general is not followed by osteosclerosis." Regardless of which is the primary process it is the replacement of marrow by fibrous tissue that kills the patient suffering with the disease.

The total amount (1,200 to 1,500 grams) of marrow in the normal individual is equal in quantity to the liver; however, perhaps less than 50 per cent of the marrow is active hematopoietically. There is probably a close correlation between the amount of active marrow replaced and the degree of anemia plus the degree of extramedullary hematopoiesis in cases of myelofibrosis. The quality or immaturity of circulating blood cells may depend upon either the damaged marrow or the extramedullary hematopoietic foci;

and in a few cases of primary myelofibrosis it is sometimes difficult to disprove the presence of a preëxisting leukemia. In the former, however, the extramedullary foci have nearly normal marrow components (normoblasts, erythroblasts, megakaryocytes, myelocytes, myeloblasts and lymphocytes), whereas in leukemia the foci consist of nests of infiltrating myelocytes, myeloblasts in myeloid leukemia, or lymphoblasts in lymphoid leukemia. In other words, the definition of extramedullary hematopoiesis is a focus of normal bone marrow components situated elsewhere than within bone and attempting to produce normal circulating red and white blood cells because of destroyed marrow, whereas the definition of a leukemic infiltration is a focus of infiltrating immature white blood cells which because of their inherent reproducing capacities produce more immature white cells (either myeloid, lymphoid, monocytoid, plasmoid). Myelopoiesis, lymphopoiesis, etc. The former is a compensatory or healing process, whereas the latter is a part of the pathological leukemic process itself.[65] It is, however, Dr. F. R. Miller's opinion that if ever extramedullary hematopoietic foci become greater in volume and hematopoietic activity than the original marrow in the bones, one must seriously entertain the diagnosis of myeloid leukemia. In polycythemia there is probably a greater quantity of active marrow than is found in the normal individual[66] and according to the above opinion the process should be classified as a type of myeloid leukemia.

Conclusions

1. Myelofibrosis may be focal or generalized and primary or secondary. Five cases of primary generalized myelofibrosis, seven cases of secondary generalized myelofibrosis, and one case of focal myelofibrosis are presented. The classification, the clinical and laboratory findings, the biopsy and autopsy findings and the treatment of these cases are presented.

2. The etiology of myelofibrosis is unknown; however, such factors as occlusion of marrow vessels, temperature, organizers and hormones may be etiological factors.

3. Testosterone was used as a therapeutic agent in four of five cases of primary generalized myelofibrosis and one of the seven cases of secondary generalized myelofibrosis. A partial remission occurred in three of the four cases of primary generalized myelofibrosis. However, it has been observed elsewhere[68] that in one case of myelofibrosis a remission occurred spontaneously. The results warrant further therapeutic trial of the use of testosterone for cases of primary generalized myelofibrosis.

4. Fibrosis of the marrow is probably much more common than is indicated by the number of published reports of these cases. The marrow of all cases of refractory anemia, particularly those with myelophthisic or leukoerythroblastic anemia, should be thoroughly studied before and after death.

5. Myelofibrosis is not similar to aplastic anemia. The marrow is

fibrotic in the former and fatty in the latter; extramedullary hematopoiesis exists in the former but not in the latter.

We wish to thank Dr. H. W. Jones, Dr. F. R. Miller and Dr. C. J. Bucher for valuable assistance.

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CASE REPORTS

SIMMONDS' DISEASE WITH THERAPEUTIC RESPONSE TO HORMONE THERAPY FOR FOUR YEARS: REPORT OF A CASE WITH NECROPSY FINDINGS*

By WARD DARLEY, M.D., F.A.C.P., ROBERT W. GORDON, M.D., F.A.C.P., and KARL T. NEUBUERGER, M.D., *Denver, Colorado*

THE recent and exhaustive review by Escamilla and Lisser [1] of the literature concerning hypophyseal cachexia (Simmonds' disease) is most timely. From this review it is apparent that confusion regarding the recognition of the syndrome has been very great. The facts that out of 595 reported cases only 101 were proved pathologically and that out of the remaining 494 cases only 158 were typical clinically bear out this contention. As a result of Escamilla's and Lisser's careful analysis of the proved cases, their definition of clinical criteria should lessen the confusion in the recognition of the condition and should serve as a more reliable background for the evaluation of therapy in such cases.

Any effort at this time to discuss the literature further would be superfluous. We do feel justified, however, in reporting a pathologically proved case of pituitary cachexia, which was carefully studied and observed over a period of years and which apparently responded to the exhibition of endocrine therapy.

CASE REPORT

The patient, a male, was treated for syphilis in 1913, at 21 years of age. In 1917 a gumma of the left testicle necessitated its removal. One year later, after a severe influenzal attack, the following symptoms gradually developed: dry atrophic skin of a peculiar lemon yellow color; loss of facial, axillary, and pubic hair with a marked thinning of the hair of the scalp and eyebrows; marked fatigability and weakness; a loss of all sexual desire and power; a hesitant, monotonous, drawling type of articulation; a marked slowing of all mental processes; a desire for extra sleep; digestive disturbances, with periods of anorexia and attacks of vomiting and diarrhea; a stooped posture and peculiar shuffling gait and, finally, a persistent anemia.

In 1920, three years after the onset of this illness, excessive thirst and polyuria developed and, after several months, seemed to be relieved and to disappear following the ingestion of large daily doses of olive oil. In 1921 a ptosis of the left upper eyelid was present for a few weeks. One year later left facial and upper extremity paralysis and numbness, together with marked headache, confusion, and aggravation of the weakness, suddenly appeared. The anemia was more marked. The serologic examinations of the blood and spinal fluid were negative. Following this upset, which gradually cleared over a period of several weeks, the condition of the patient remained as before, until 1931. At this time two teeth were removed with resulting persistent hemorrhage and aggravation of the anemia. For a time the patient was in a criti-

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From the Departments of Medicine and Pathology, University of Colorado School of Medicine and Hospitals.

cal state. Subsequent improvement from this setback was slow and the patient's condition, as compared with the previous level, never was as good.*

We first saw this patient September 24, 1936, when he was 44 years of age. He had been confined to bed for several days because of progressive weakness, dependent edema, vomiting, and somnolence. He was aroused with difficulty and was irritable and petulant whenever disturbed. Generalized pitting edema was present, most marked in the lower limbs. The skin generally was of a lemon-yellow color, dry, cool, and of a parchment-like consistency; that below the knees was covered with a weeping eczematoid eruption. Pubic, axillary, and facial hair was absent and the hair of the scalp was thin and exceedingly fine. The eyebrows were almost absent and very few eyelashes were present. The facies was expressionless and mask-like. The right pupil was larger than the left; both reacted to light and accommodation. Many of the remaining teeth were carious; the gums were retracted, congested, and bleeding. The heart sounds were distant and a soft apical systolic murmur was audible. The heart was not enlarged. The penis and scrotum were infantile. The left testicle was absent; the right was about one-fourth normal size and of abnormally soft consistency. No prostate gland could be palpated by rectal examination. Neurologic examination revealed nothing abnormal. The body weight was 136 pounds, the total temperature 97° F., the respiratory rate 14, the pulse rate 80, and the blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The hemoglobin was 12.2 grams (Sahli), the red cell count 2,850,000 and the white cell count 4,000, with 56 per cent polymorphonuclear neutrophiles, 29 per cent lymphocytes, 7 per cent mononuclear cells, 6 per cent eosinophiles, and 2 per cent basophiles. The blood Wassermann reaction was negative. The fasting blood sugar was 75 mg. per 100 c.c. of blood. The bleeding and coagulation times were normal. Urinalysis revealed nothing abnormal. The basal metabolic rate was minus 35. The only abnormality revealed by the electrocardiogram was a very low voltage in the classical leads (figure 1).

Four grains of desiccated thyroid (USP), 45 grains of ferrous sulphate, and 150 units of liver extract by intramuscular injection were given daily. After three weeks the patient was very little, if any better, as was no more than to be expected, since this treatment represented much the same type of régime that had been prescribed frequently over the preceding years. On October 14, the liver was discontinued, the thyroid dosage was reduced 50 per cent, and the patient began to receive 150 units of anterior-pituitary-like hormone† intramuscularly once daily. Within one week definite improvement was apparent: the urinary output increased greatly and at the same time the edema rapidly diminished; in five days the weight dropped from 136 to 112 pounds; the mental picture improved and somnolence disappeared; the vomiting ceased and a desire for food returned; the gums stopped bleeding; the strength improved, and the patient became able to get out of bed. By the end of the week generalized superficial desquamation was marked. On October 27, the thyroid was discontinued and the pituitary substance was thence administered only every other day.

By January 18, 1937, improvement, though slow, had continued sufficiently that the dosage of pituitary substance was reduced to 150 units twice weekly. On this date the hemoglobin was 12.6 grams (Sahli) and the red cell count 4,800,000. A fractional gastric analysis gave results within normal limits. The fasting blood sugar was 70 mg. per 100 c.c. of blood. An attempted glucose tolerance test was unsuccessful because the patient was unable to retain the glucose. A routine spinal fluid examination yielded normal findings. The body weight was still 112 pounds. The yellowish pallor was little, if any, improved and the skin retained its parchment-like consistency and appearance. The hair growth was unchanged and the external

*The clinical notes from 1920 through 1931 were taken from the case records of the late Dr. Sherman Grant Bonney.

†Squibb Follutein.

genitalia appeared in no way altered. Sexual desire and power had not returned. In every other way improvement seemed marked: the voice and facial expression were more animated; strength and energy had greatly increased, although the gait

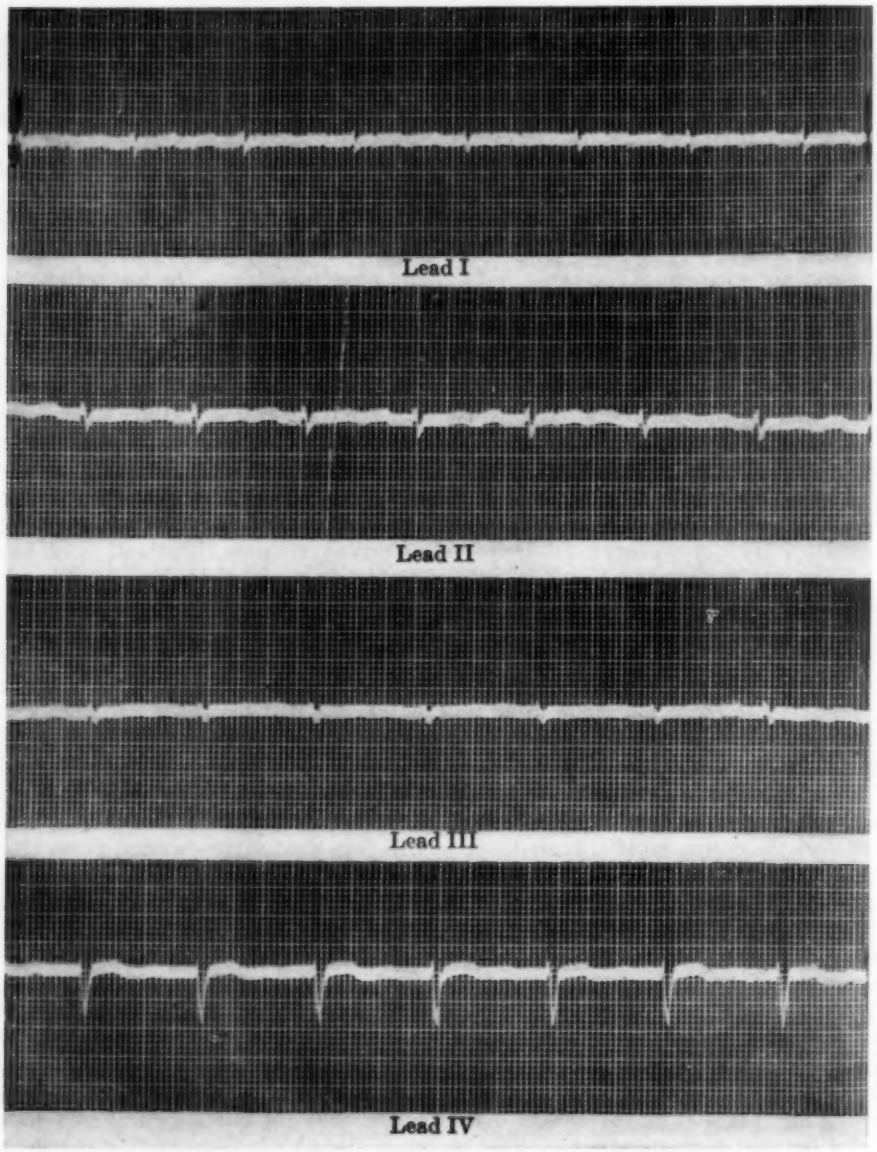

FIG. 1. Electrocardiogram—low voltage in first three leads.

was still shuffling in type; the attacks of indigestion no longer occurred and the appetite remained better; the patient's disposition was amiable, his mental processes were greatly improved, and his desire for sleep was less, with an average sleep of 12 hours

out of 24. On February 1, 1937 the patient returned to work, from which he had been absent since September 1, 1936, and which was not difficult (operation of a mechanical coin-counting device). He began to regain weight: 120 pounds was the body weight by March 1, 127 by April 1, and 133 by May 1.

In October 1937, after one year's treatment, examination indicated that the patient apparently had held his gain. He had missed no further time from work. He was still receiving two injections of pituitary-like substance a week. His weight was 130 pounds, blood pressure 110 mm. Hg systolic and 80 mm. diastolic, basal metabolic rate minus 53, hemoglobin 14 gm. (Sahli), red cell count 3,390,000, and white cell count 6,080, with a differential count of 70 per cent polymorphonuclear neutrophiles, 25 per cent lymphocytes, and 5 per cent eosinophiles.

During the next three years the patient was seen only quarter-annually and seemed to be holding his own, but by January 1940 the patient and his family had become dilatory and dosage frequency had become sporadic and irregular. By May 1940 it was apparent that the patient was failing; because of weakness, somnolence and mental sluggishness he stopped work. By December 1940 he was again confined to bed; he was edematous, stuporous, and having much vomiting. In January of 1941 hospitalization was necessary. At this time, fibrillation and anasarca were present. The hemoglobin was 10 grams (Sahli), the red cell count 3,790,000 and the white cell count 5,600, with 60 per cent polymorphonuclear neutrophiles, 34 per cent lymphocytes, 3 per cent large mononuclear cells, and 3 per cent eosinophiles. The blood non-protein nitrogen was 25 mg., the creatinine 1.37 mg., and the sugar 50 mg. per 100 c.c. of blood. A transfusion, digitalization, thyroid, and pituitary-like substance seemed to do very little, if any, good. Intravenous salyrgan at biweekly intervals increased the fluid-output, but marked congestive failure persisted. For the three months prior to the death of the patient on August 8, 1941, all intensive therapy was discontinued.

The necropsy was performed after embalming. The body was fairly well nourished, the skin was pale, axillary and pubic hair were missing, and the arms and legs were edematous. The panniculus adiposus measured 1 to 2 cm. in thickness. Neither pituitary nor thyroid could be discerned with the naked eye. The adrenals were scarcely half the normal size, as was the right testicle, which appeared to be diffusely fibrosed. The prostate gland was almost invisible grossly. The heart showed an old rheumatic mitral valvulitis, with a few recent verrucous vegetations; the left ventricle was dilated. The liver was atrophic and displayed several shallow scar-like indentations on the anterior surface. The pancreas was rather small and somewhat interspersed with fat and fibrous tissue. The arterial system was elastic and free from arteriosclerosis and from lesions suggesting syphilis.

Microscopically, the fibrous contents of the sella turcica failed to show any trace of pituitary tissue of either anterior or posterior lobe. There was nothing but poorly nucleated scar tissue in which were a few vascular areas containing occasional fibrocytes and round cells (figure 2).

The thyroid was extremely atrophic. Sections taken from its presumable site showed islands of lymphocytes separated by cords of connective tissue. Within these islands a few undersized thyroid follicles were arranged singly or in small groups; occasional follicles were scattered through the strands of connective tissue. The follicles were lined with flattened or low-cuboidal epithelium; their lumina were either empty or contained a small amount of pinkish colloid (figure 3).

The parathyroids, two of which were found and examined, showed well-preserved, water-clear cells and occasional oxyphilic cells. They appeared generally normal.

The adrenal cortex was atrophic and its layers were poorly demarcated. In several places fibrous strands arising from the thickened capsule overlapped and partly replaced the zona glomerulosa (figure 4). The lipoid contents were poor and

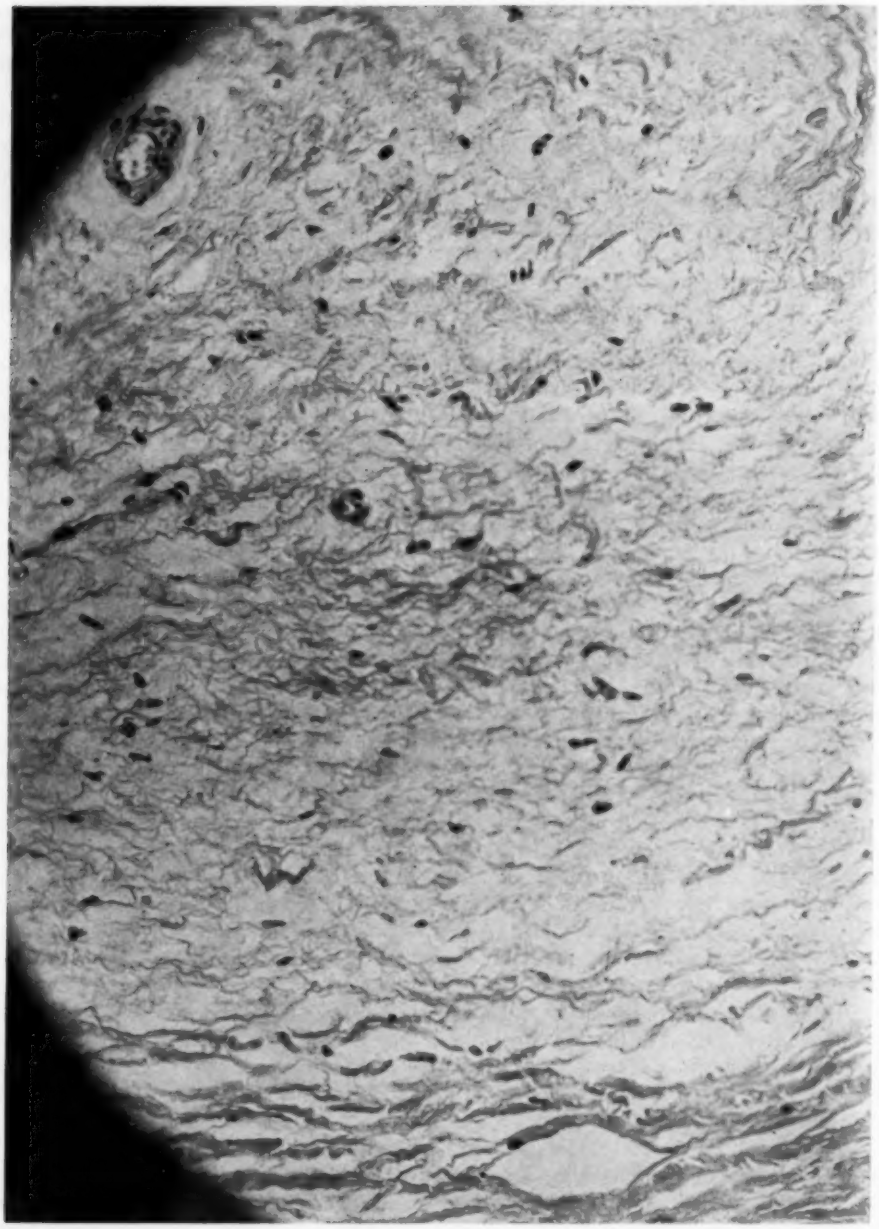

FIG. 2. Obliterated pituitary.

irregularly distributed. Capillaries were dilated. The medullary tissue in some portions was greatly reduced and fibrosed; in other portions it was rather well preserved. Occasional areas, especially in the medulla, were infiltrated with lymphocytes.

The prostate consisted of small bundles of smooth muscle, interspersed with con-

nective tissue; it contained only a very few small glands, lined with low-cuboidal epithelium (figure 5).

In the testicle no normal tissue was evident. The tubules were sparse, distorted, small, and hyalinized. Several of them formed solid strands with small round nuclei in the center; most tubules, however, were anuclear. Basement membranes were thickened. The intertubular spaces were very wide and were composed of loose, poorly nucleated connective tissue. No Leydig cells were present (figure 6). The epididymis was much better preserved anatomically; the ducts, however, had very narrow lumina.

The pancreatic tissue, though interspersed with connective tissue and some fat, was, on the whole, well preserved.

Other findings included brown atrophy, splitting, and occasional basophilic degeneration of heart muscle fibers*; brown atrophy of the liver; moderate atrophy of the gastric mucosa; hemosiderosis of the spleen, which had large Malpighian corpuscles. The remaining findings in the visceral organs were insignificant; there was no characteristic lesion of the bone marrow.

The brain showed essentially well-preserved cortical architecture. The number of nerve cells appeared about normal. Some of the cells exhibited more or less marked degenerative changes, such as paleness and vacuolation; others displayed a darkly basophilic, shrunken cytoplasm. There was little or no reaction of the supporting tissues. The thalami and the nuclei of the interbrain showed occasional ghost cells or blanched cells with faded outlines, increased wear-and-tear pigment in some of the neurons, and slight swelling of some of the oligodendroglial cells and astrocytes. These changes, altogether not conspicuous, were scattered over the centers mentioned above and were not accentuated in any one specific gray nucleus. "Senile" plaques and fibrillary alteration were absent (figure 7).

Escamilla and Lisser conclude from their review that Simmonds' disease is characterized by four cardinal signs: weight loss, asthenia, impotence, and low metabolic rate. It is difficult to determine the true significance of the varying weights in this patient. His average weight in health had been 140 pounds; between the onset of his illness and the time he first came to us, the weight had varied between 130 and 135 pounds. When the patient was first examined by us, however, he was very edematous; he rapidly lost 24 pounds as a result of the diuresis which followed the institution of therapy: the resultant 112 pounds in all probability represented his true weight. The low gain which subsequently occurred was, in all probability, the result of improving general condition. Asthenia was a marked feature in the case, particularly before therapy was started, and also later when treatment was apparently inadequate. The patient lost all sexual desire and power soon after the onset of his symptoms. The initial basal metabolic reading was minus 35. It is of interest that one year later, after clinical improvement had been so marked, the rate was minus 53.

Many other findings peculiar to the syndrome of pituitary cachexia were manifest in our case. Apathy, dullness, and drowsiness, although variable in degree, were always prominent. The body surface always felt abnormally cool to the touch but, curiously enough, the patient himself rarely complained of being chilly. The oral temperature was always subnormal but was never markedly low: it ranged from 97 to 98° F. The skin was always dry; pallor always was present. The absence of axillary and pubic hair was typical. The thinning of

* "Basophilic degeneration" of the myocardium appears to be particularly frequent in diseases of the endocrine glands, especially of the thyroid.

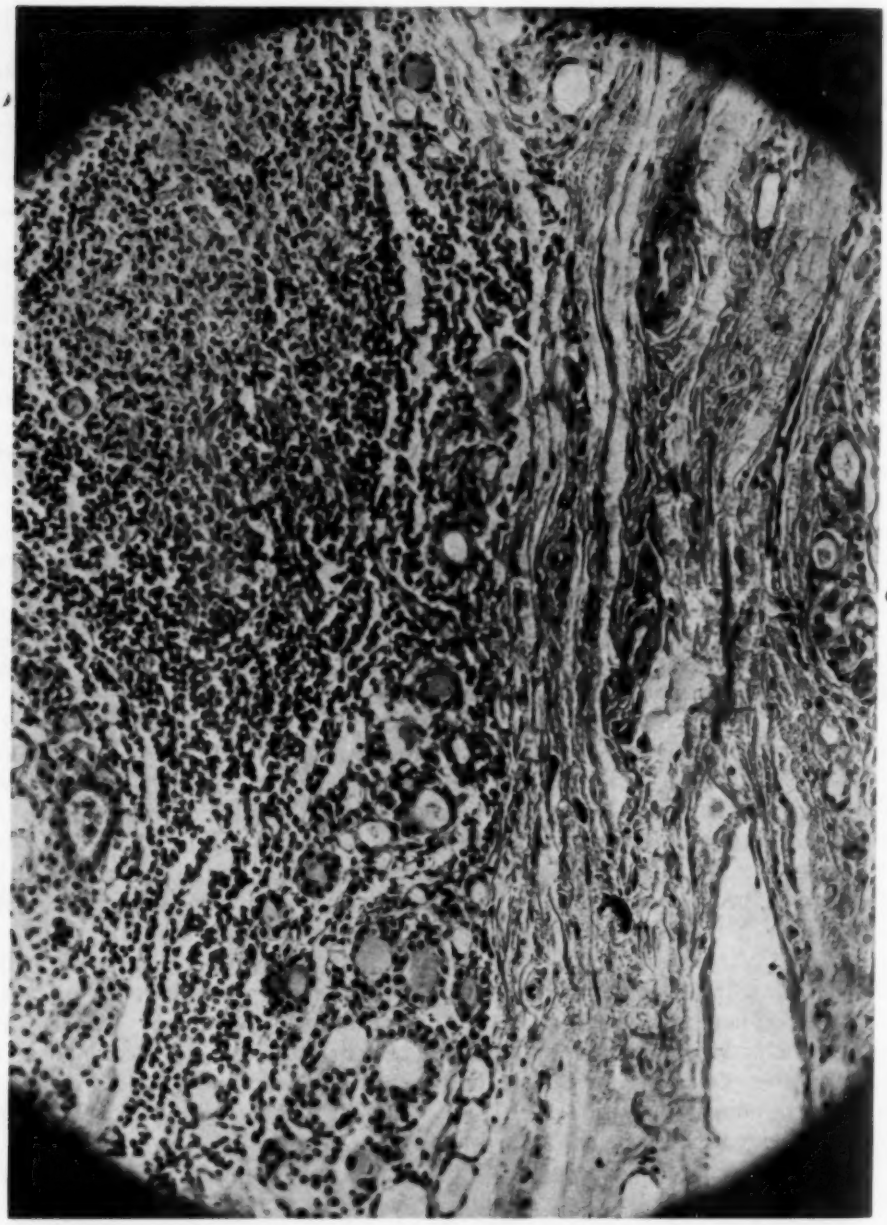

FIG. 3. Sclerosis of thyroid; large island of lymphocytes; scattered atrophic follicles.

the hair of the scalp, face, and eyebrows and the dental caries, frequently noted in the literature, were present. Genital atrophy was pronounced and apparently was more marked than that noted in most male patients suffering from this illness. Disturbances in water balance, commonly found in the condition, were evident throughout the patient's illness. Three years after symptoms appeared,

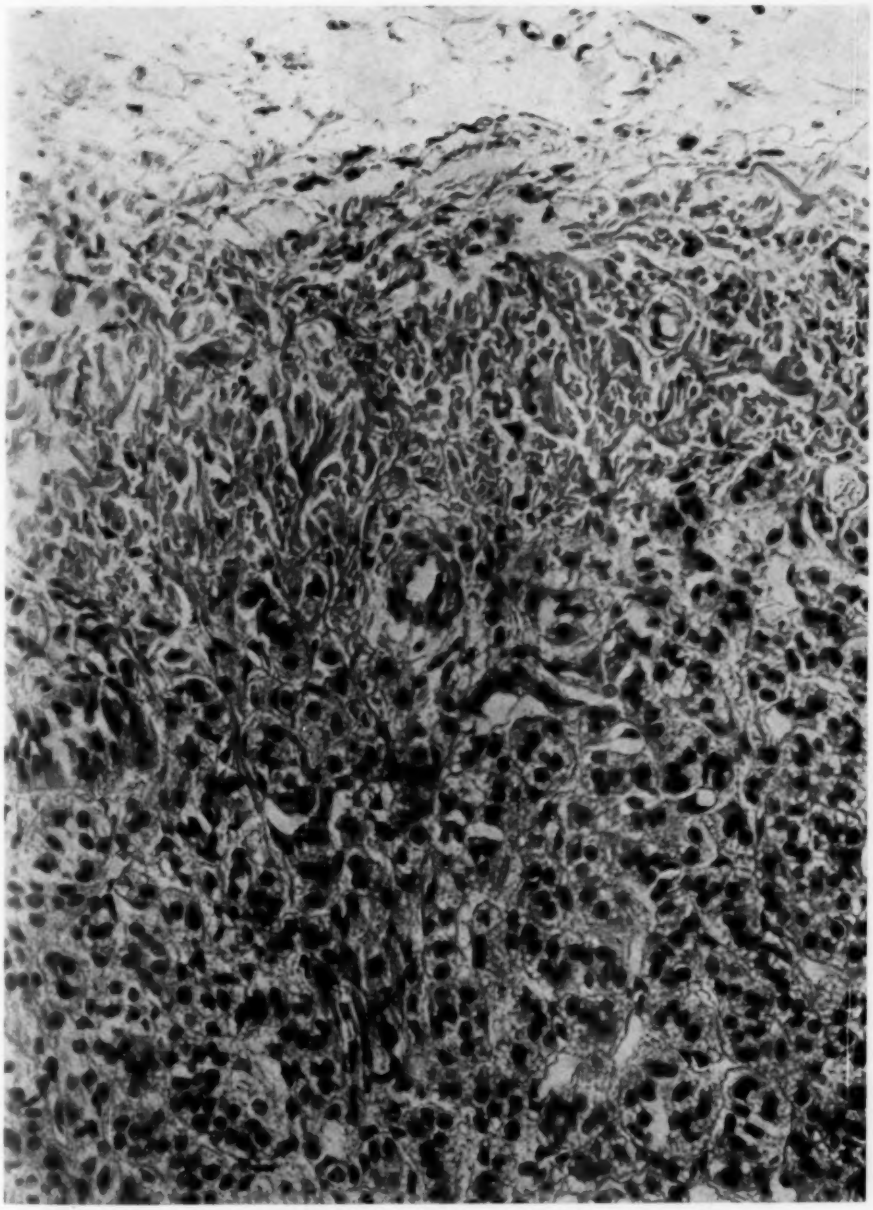

FIG. 4. Adrenal cortex with fibrosis of zona glomerulosa.

a picture like that of a diabetes insipidus was present for a few weeks. Escamilla and Lisser found such a picture to be present in 15 per cent of the group of pathologically proved cases. Edema of noncardiac origin was marked at the time of our first contact with this patient. Finally anasarca, characteristic of cardiac decompensation developed, would not respond to any type of therapy, and was

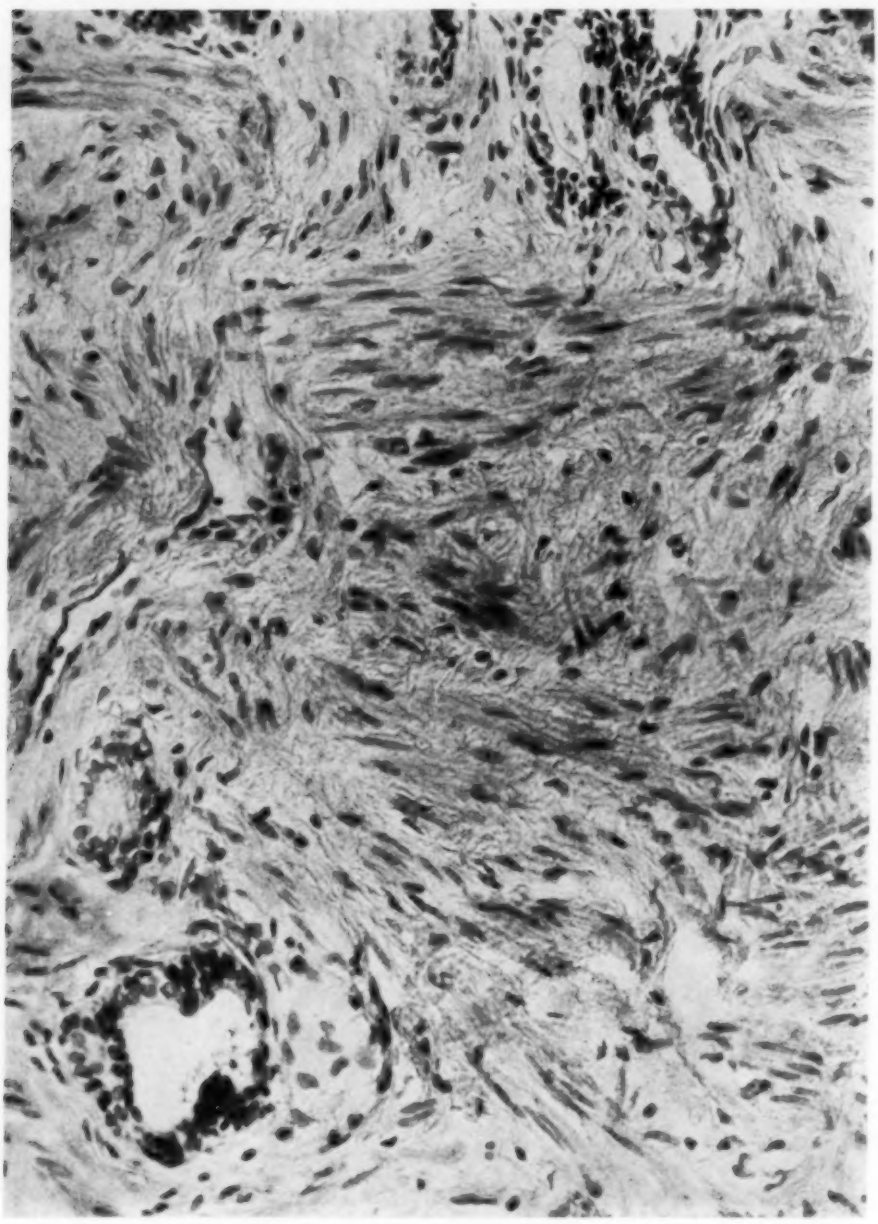

FIG. 5. Atrophy of prostate.

the ultimate cause of death. Emaciation, present in most cases, was never marked in this patient; it probably was masked to some degree by edema of one type or the other. Abnormally slow pulse rates and low blood pressures were thought by Escamilla and Lisser to be of significant frequency, but such were not displayed by our patient.

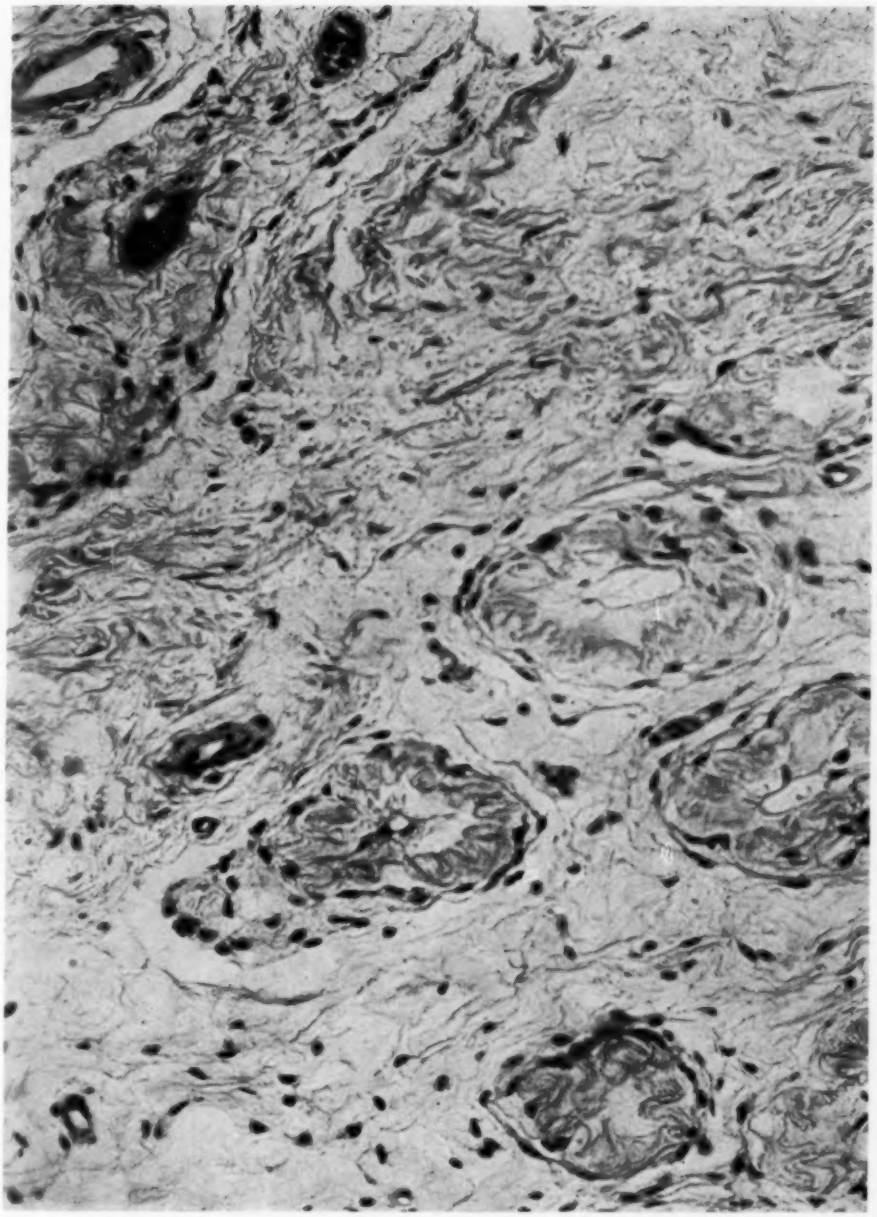

FIG. 6. Sclerosis of testis, with almost complete obliteration of tubules.

The laboratory findings in our case tended to be consistent with the findings usual in Simmonds' disease. The low basal metabolic readings have been mentioned. The fasting blood sugar levels became progressively lower as the disease progressed. The anemia was apparently of the type and degree commonly found. Escamilla and Lisser noted the frequent reporting of an increased eosinophile

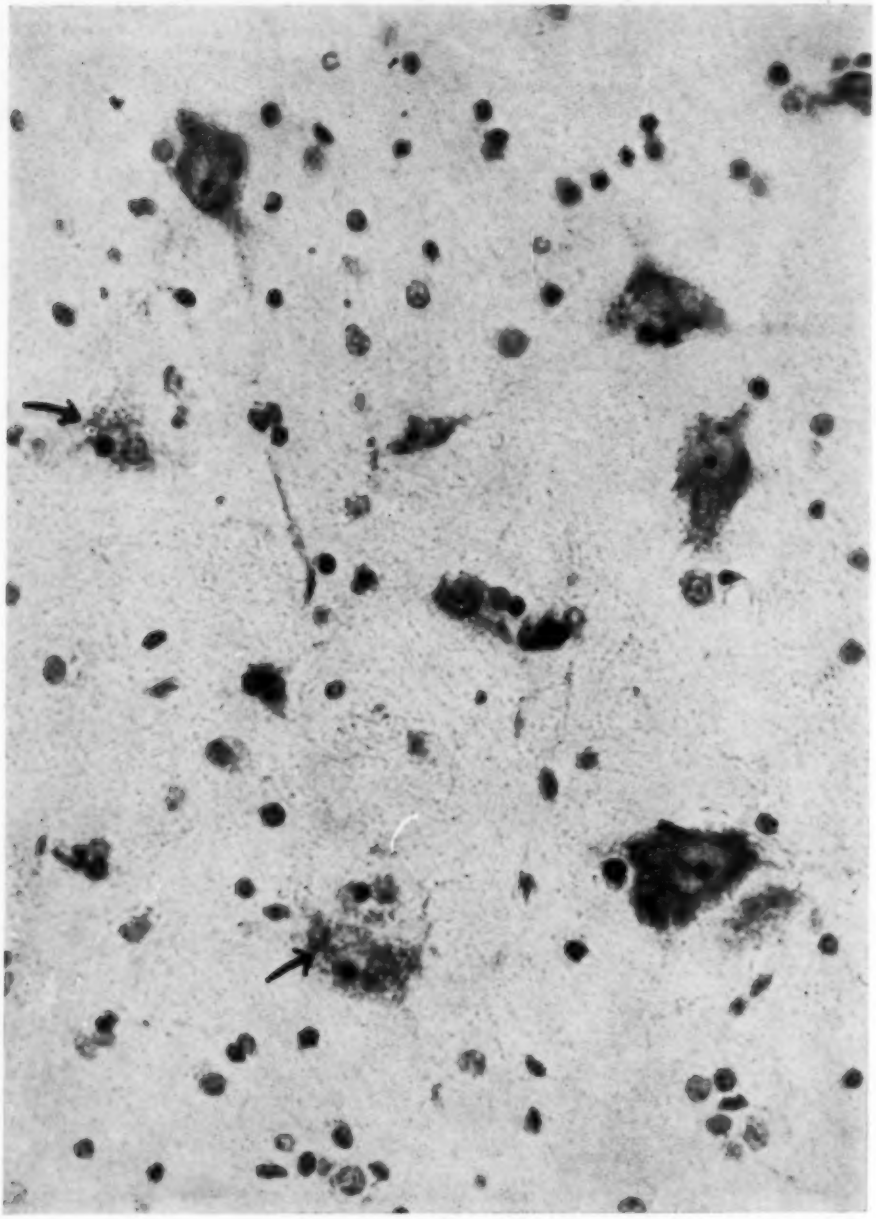

FIG. 7. Degenerating nerve cells in the nucleus supraopticus.

percentage but in our case, out of many differential blood counts, an eosinophilia of 5 per cent or more was found only twice, both times early in our observation period. The gastric acidity was within normal limits as were also the routine blood chemistry findings obtained a few months before death.

Since the 101 cases of pathologically proved Simmonds' disease all represented

fatalities, Escamilla and Lisser, in their effort to glean evidence as to the efficacy of therapy, had to deal almost exclusively with the 158 cases which were typical from the clinical standpoint. Of this group 60 per cent appeared to improve as the result of therapy. After consideration of the difficulties in the evaluation of treatment, they concluded that "however conservative or skeptical one may be, a careful reading of many of the protocols forces one to believe that in some cases specific pituitary therapy must be given credit for the extraordinary improvement which occurred."

For a period of four years our patient appeared to respond to the administration of anterior pituitary-like substance. The rapid change in the patient, particularly early in therapy, was dramatic. We do not feel that simple suggestion could have been a factor in this improvement because at the time pituitary therapy was initiated, the patient was semistuporous and did not know or care about what was being done for him. Although sustained improvement seemed so definite, it must be stated, in all fairness, that this patient's condition was never such that a diagnosis of Simmonds' disease was not apparent. We do feel, however, that as a result of the specific pituitary therapy, not only was the patient elevated to a higher plane of activity and well being but his life was prolonged by several years.

The pathologic classification of this unusual condition in a middle-aged male, without definite cachexia, is associated with the same difficulty that is encountered in many related cases, namely, the differential diagnosis between Simmonds' disease and Falta's disease (pluriglandular sclerosis). This problem has been discussed by many authors, among them Berblinger,[2] Meerwein,[3] and Castleman and Hertz.[4] The latter co-authors pointed out that if some "glands are sclerotic and others only atrophied, one might assume a primary lesion in one of the sclerotic glands and secondary atrophy of the others." In the case under discussion, the destruction and fibrosis of the pituitary, including the posterior lobe, were so thorough as to make it impossible to find any trace of the original tissue. Although the adrenals and prostate showed atrophy mainly, though not exclusively, the thyroid and testis exhibited sclerosis predominantly; this was, however, not quite as far advanced as that in the pituitary. One may therefore conjecture that the hypophysis was the organ primarily involved, and that its destruction caused atrophy and sclerosis of the remaining glands. Succinct histologic proof, however, cannot be given. The final outcome of this disease of 23 years' duration was a pluriglandular sclerosis, of which the primary site and ensuing course cannot be traced dependably and irrefutably. Because of the close relationship between Simmonds' and Falta's diseases, considered as possibly identical by some authors (Hirsch and Berberich[5]), the pathologic classification in our case appears to be of minor importance.

The etiology is questionable but three causative factors should be considered: influenza, rheumatism, and syphilis. The symptoms developed after a severe attack of influenza. In this disease inflammatory processes in the hypophysis are not uncommon (Berblinger[2]). However, such severe sequelae as encountered in this case are extremely rare. The rheumatic heart disease, evidenced only at autopsy, might have given rise to embolic damage of the pituitary. This assumption, however, appears remote since infarcts and their sequelae were missing in other organs and since a rheumatic etiology for Simmonds' disease has only ex-

ceptionally been demonstrated in the literature. Syphilis may play an important rôle in Simmonds' disease (Berblinger,[2] Jaffé,[6] and others). The early history of our patient points in this direction. It is apparent, however, from observation of the earlier available records and also from our own records that our patient failed to show either clinical or serological evidence of syphilis. Moreover, at necropsy, syphilitic manifestations were missing, unless the scars on the surface of the liver are considered to be of syphilitic origin, a possibility which can be neither denied nor proved. The sclerosis of the testis was in all probability a manifestation of the pluriglandular sclerosis and not one of syphilis, because the latter rarely leads to such pronounced shrinkage and homogeneous obliteration with disappearance of the interstitial cells.

The brain changes in our case were not serious and not especially characteristic. However, the scattered degenerative lesions of neurons and the glial reactions, particularly in the nuclei of the thalami and interbrain, are worth mentioning. They may have been secondary to the pluriglandular insufficiency, especially to the destruction of the posterior lobe of the pituitary. This belief was held by Gallavan and Steegmann,[7] who reported similar findings several years ago. The number of cases with thorough histologic examination of the central nervous system is still small. Further investigation of such cases is desirable.

Summary

The case of a male patient, displaying the clinical and laboratory characteristics of Simmonds' disease, is presented with the following features:

(1) a clinical course of 23 years' duration;

(2) an apparent therapeutic response to the administration of anterior-pituitary-like substance for four years;

(3) necropsy findings, which revealed complete obliteration of the pituitary, marked sclerosis of the thyroid and testis, and atrophy of the prostate and adrenal, together with moderate degenerative changes in the brain, particularly in the thalami and the interbrain.

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ELECTROCARDIOGRAPHIC RECORD OF A DYING HEART*

By SOLOMON KRELL, M.D., *Bronx, New York*

CASE REPORT

MRS. E. R., a 74 year old female, was admitted to the Hospital and Home of the Daughters of Jacob on November 21, 1940, for custodial care. The diagnosis on admission was general arteriosclerosis, coronary sclerosis, and bilateral cataracts. Her chief complaints were those of general weakness, and occasional fainting spells. Examination of the heart revealed poor heart sounds, a regular rhythm, and a blood

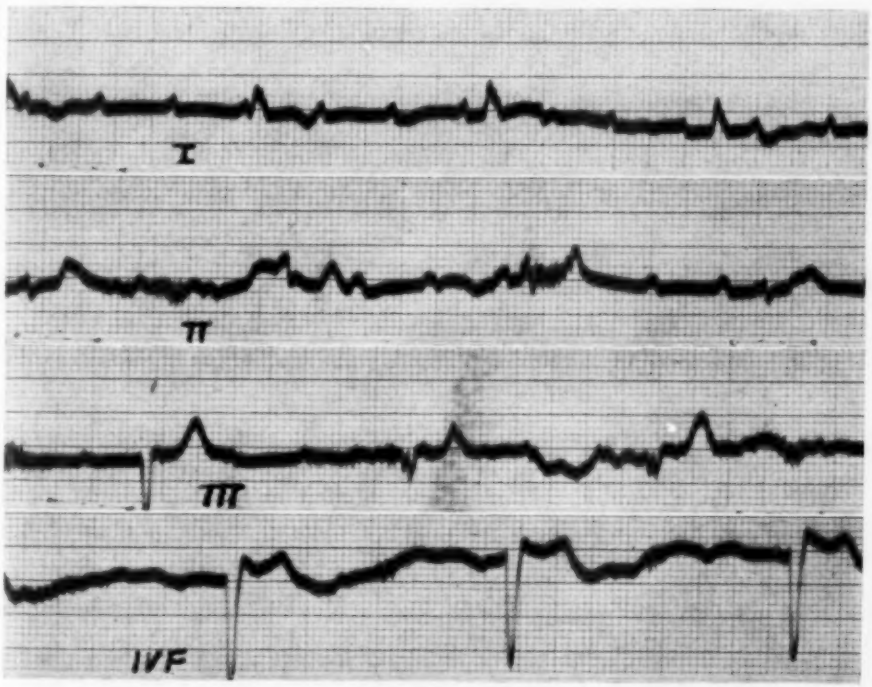


FIG. 1. Following cardiac standstill of 1¼ minutes, 1 c.c. of epinephrine (1–1,000) intracardially. Tracing taken within a few minutes. Complete A–V dissociation but no coupling.

pressure of 180 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram taken on December 2, 1940, revealed a 2:1 A–V block, slurring and notching of the QRS complexes, a depressed ST_2, inverted T_3 and T_4, and a deep Q_4.

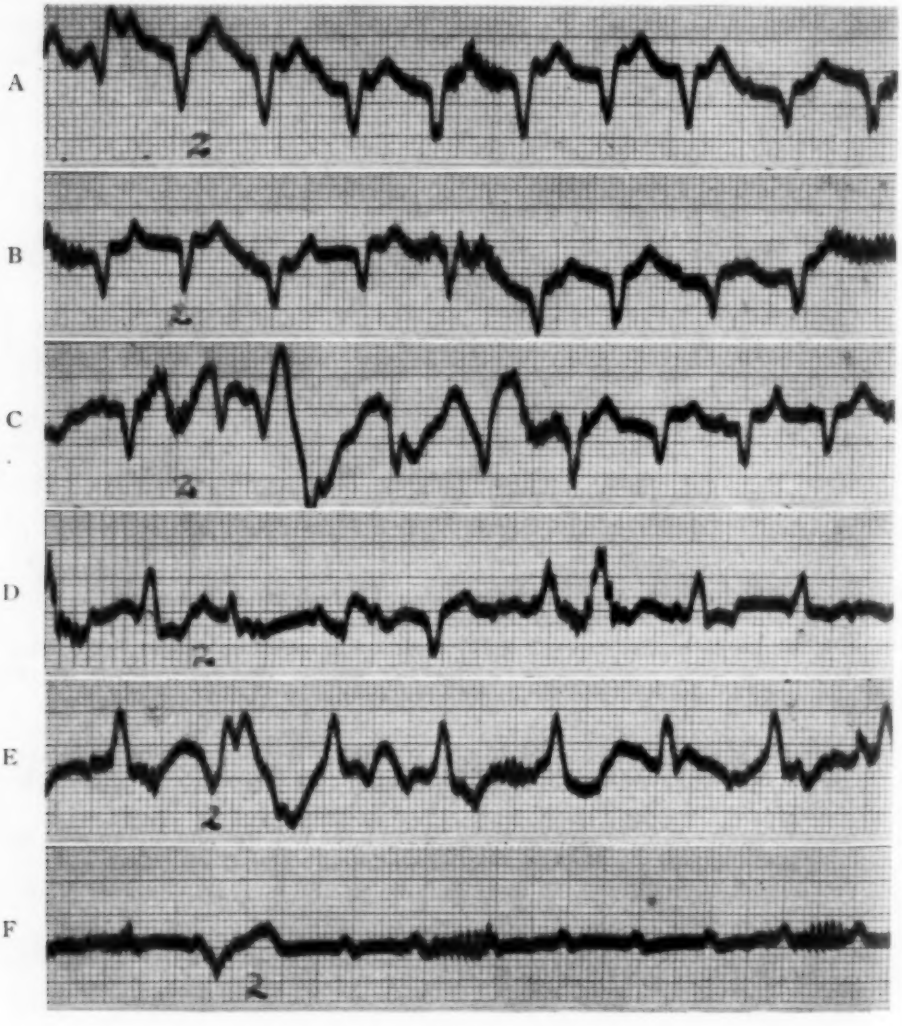
Between January of 1940 and February of 1942, she had frequent dizzy spells and complained of occasional precordial pains and weakness. Her blood pressure ranged from 140 mm. Hg systolic and 70 mm. diastolic to 180 mm. systolic and 70 mm.

* Received for publication January 21, 1943.
From the Hospital and Home of the Daughters of Jacob, New York, N. Y. From the service of Dr. A. A. Brill and Dr. A. S. Hyman.

diastolic. There was nothing noteworthy in the examinations of the blood and of the urine.

On February 8, 1942, she was admitted to the hospital with a temperature of 101° F., and a diagnosis of acute upper respiratory infection was made. Shortly after admission, she had a sudden sinking spell. Her pulse was rapid, and the blood pressure at that time was 170 mm. Hg systolic and 100 mm. diastolic. The following day an electrocardiogram showed complete A–V dissociation with a coupled rhythm. She was complaining of severe dizziness. There was moderate orthopnea as well as cyanosis of the lips. The lungs were clear. The heart showed considerable enlargement to the left, with the heart sounds weak; the rhythm was coupled with a total rate of 30 to 35. Neither the liver nor the spleen was palpable. She was given aminophyllin intravenously and placed on ephedrine, gr. 3/8, every three hours.

On February 17, 1942, her condition was much worse. There was marked cyanosis and restlessness, with Cheyne-Stokes respiration. Complete heart block and coupled rhythm persisted. During an examination, the patient suddenly began to



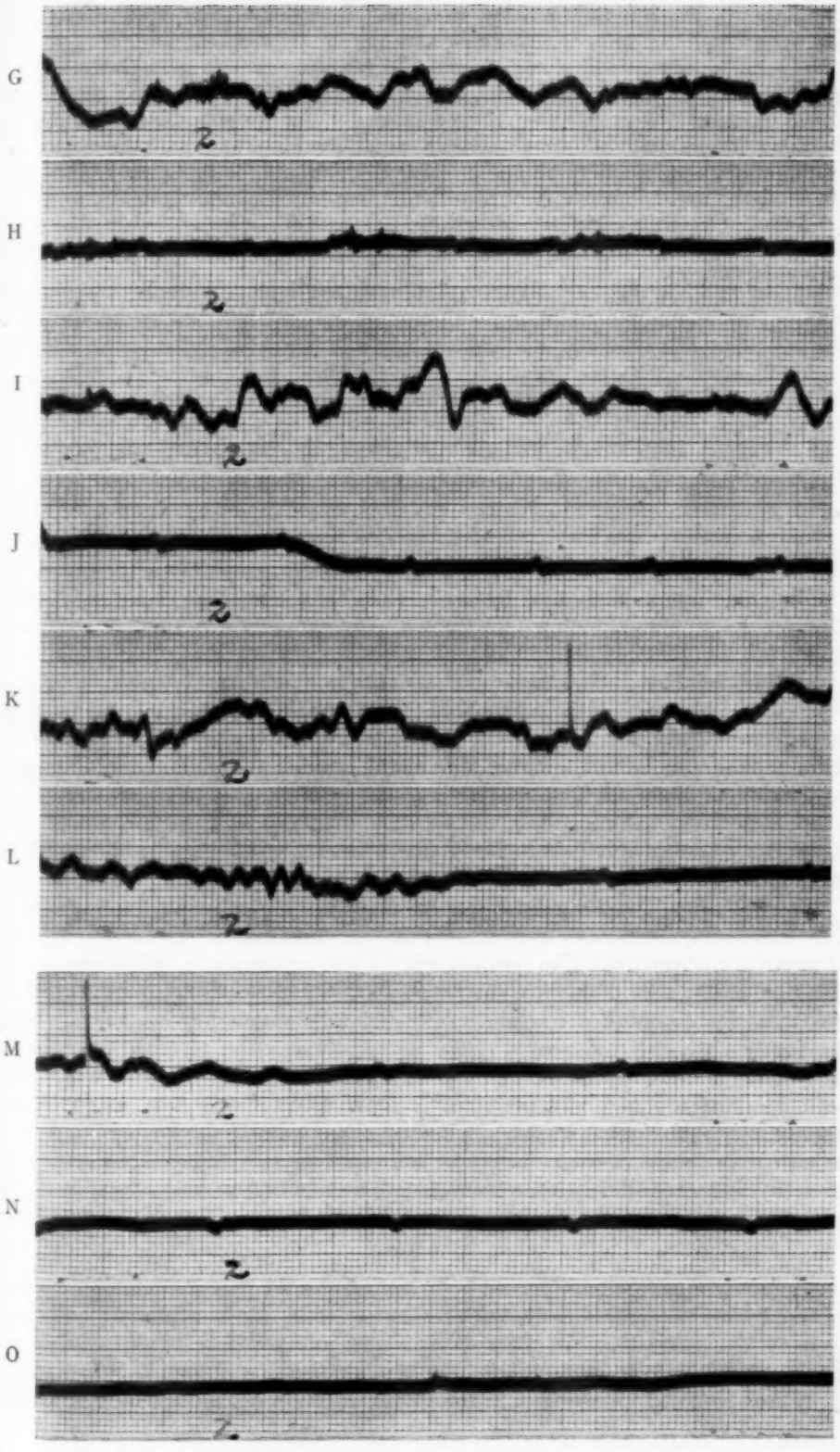


FIG. 2. Continuous strip of Lead II (A–O) following a convulsive seizure.

struggle, turned a deep purple, and both heart and respiration stopped. Following cardiac standstill of one and a quarter minutes, she was given 1 c.c. of epinephrine (1–1,000) intracardially. Cardiac activity was once more resumed, she began to breathe again, and her color was improved. An electrocardiogram taken within a few minutes showed complete A–V dissociation, but no coupling (figure 1).

Twenty-four hours later the patient had a convulsive seizure. When that subsided, a continuous strip of Lead II was taken until the time of death, which followed in about 10 minutes.

It will be noted that strips A, B, C, D, E, and F, show ventricular tachycardia with runs of ventricular fibrillation. At the end of strip E, heart sounds were no longer audible, and clinically, the patient was pronounced dead. Electrical activity continued, however, in the form of ventricular fibrillation (strips G, I, K, L), punctuated by long pauses of ventricular standstill, while the auricles continued to beat regularly (strips H and J). In strips K and M, there appears a single normal QRS complex. There is persistent auricular activity at a diminishing rate, long after all semblance of ventricular activity had ceased.

Discussion

Records of the dying heart have appeared in the literature from time to time. The first one was published by Rohmer [1] in 1911. Since then, numerous other observers have published electrocardiograms taken at or near death. To mention only a few, in 1923 Schellong [2] reported 20 cases; the following year Kahn and Goldstein [3] reported their observations on the dying heart; Willius [4] wrote in 1930, Jezer, Master and Schwartz [5] in 1936, and Formigne [6] in 1938. All of these records show abnormalities of rhythm and QRS complexes. The rhythm abnormalities run from complete A–V dissociation through ventricular tachycardia to ventricular fibrillation and standstill. Some cases have been reported where ventricular activity ceased before that of the auricles, and in others, the sequence was reversed. In the case reported upon here, the auricles showed electrical activity for at least 10 minutes after ventricular standstill.

Jezer, Master, and Schwartz [5] stressed the danger of epinephrine in cases of complete A–V dissociation, explaining that this drug has a tendency to initiate ventricular tachycardia. Our patient lived for 24 hours following intracardial injection of 1 c.c. of 1–1,000 epinephrine. During these 24 hours the rhythm was that of complete heart block, but, curiously, the coupling which had been previously observed disappeared. We doubt whether the terminal ventricular tachycardia and fibrillation were in any way related to the epinephrine which had been administered 24 hours previously. Obviously, in this case, as in others elsewhere reported, some irritable focus or foci were established, which took precedence over the previously functioning idioventricular rhythm. Thus, ventricular tachycardia and fibrillation were initiated, terminating in cardiac standstill.

Summary

An electrocardiographic record is presented of a 74 year old female who had suffered some two years before death from arteriosclerotic heart disease and complete A–V dissociation. In the course of an acute upper respiratory infection, she developed cardiac standstill for one and one-quarter minutes. Cardiac activity was resumed following an intracardiac injection of epinephrine. Twenty-

four hours later, she developed ventricular tachycardia, ventricular fibrillation, and cardiac standstill.

I wish to acknowledge with thanks the aid extended to me by Bernard Newman, B.S., Ch.E., in charge of the pathology laboratories at the Hospital and Home of the Daughters of Jacob.

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WOLFF-PARKINSON-WHITE SYNDROME SIMULATING MYOCARDIAL INFARCTION *

By HERBERT EICHERT, Lieut. (M.C.), U.S.N.R., *Boston, Massachusetts*

THE purpose of this paper is to report a case of the so-called Wolff-Parkinson-White syndrome, a relatively benign cardiac abnormality, which simulated and was misinterpreted as myocardial infarction.

Characteristic electrocardiograms appeared in the literature many years ago,[1, 2] but their significance and the various features of the syndrome were first clearly defined by Wolff, Parkinson, and White in 1930,[3] and the relative benignity of the condition established. Numerous subsequent publications [4, 5] have appeared in journals of limited circulation and consequently the knowledge of this syndrome has not been widely disseminated.

CASE REPORT

R. W., a salesman, was 40 years old at the onset of his illness in 1932. During this illness he resided in several different cities and the material here presented is an aggregate of the observations of various physicians who attended him, in addition to the studies of the author during the latter part of this period.

He was in good health up to the onset of the present illness. During his youth, he indulged freely in athletics and never had any symptoms which prompted him to restrict physical activity. During adult life he worked actively at his occupation, and was never aware of any undue shortness of breath or heart consciousness.

In the spring of 1932, during a period of emotional strain, and after an unusually heavy session of handball, he "wilted" and was seized with an intense pain in his

* Received for publication February 9, 1944.

chest accompanied by dyspnea. He went home and to bed but did not feel it necessary to call a physician. Although the symptoms gradually subsided, he was unable to sleep until 10 hours later, when the pain disappeared. The following day, he felt washed out and under par, but was able to carry out the usual duties of his occupation.

After several days of continued "ill health," he decided to seek medical attention and was studied in the Out-Patient Department of a large hospital. The general physical examination is said to have been negative at the time, but the electro-

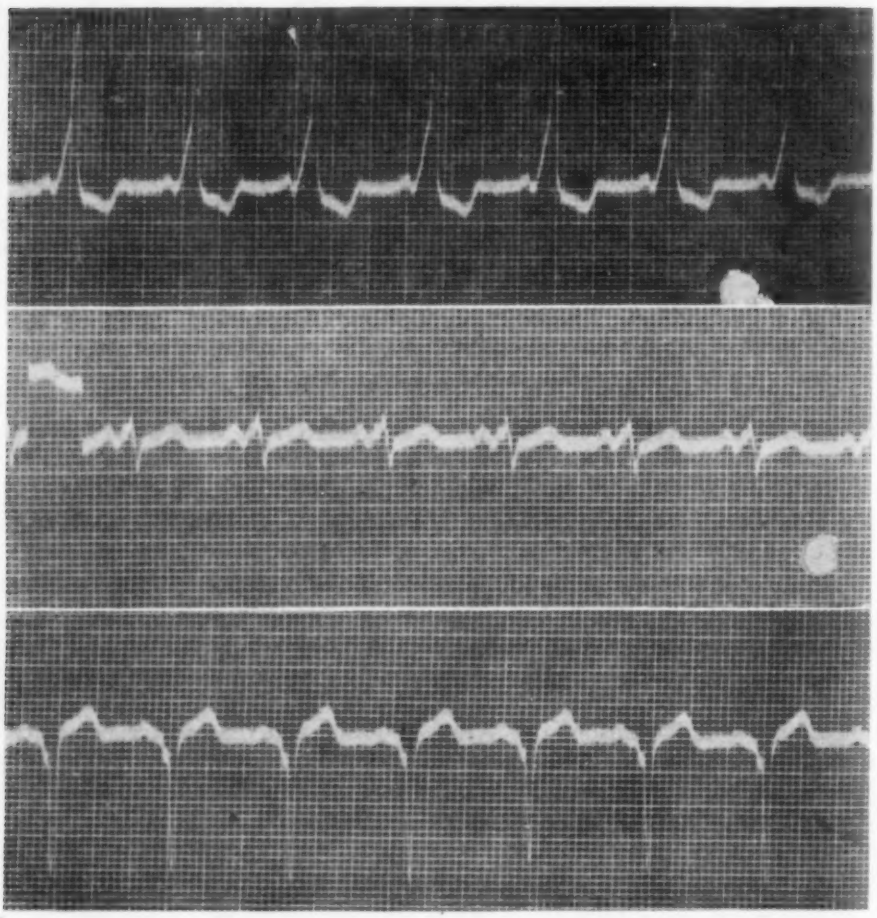

FIG. 1. Typical initial electrocardiogram on patient demonstrating the important features of the Wolff-Parkinson-White type of tracing. Viz: P–R interval of 0.1 sec. or less, slurring and widening of the QRS with T waves opposite main ventricular deflection.

cardiogram was abnormal. This electrocardiogram is now unobtainable, but the description suggests that it is identical with subsequent tracings. Such a typical tracing is reproduced in figure 1. These bizarre findings were interpreted as indicating coronary insufficiency with atypical bundle branch block.

The patient was cautioned against physical overexertion, but was permitted to return to his work. He continued to have transient episodes of breathlessness, precordial distress and palpitation, and these symptoms became worse during the ensuing

year. Nervousness and apprehension became a problem of growing concern until finally he spent most of the day in bed in an effort to alleviate his symptoms. For almost a year he remained practically bedridden. Available fragmentary medical records covering this period indicated that his physical status remained essentially unchanged and the electrocardiographic tracings continued to be identical with those previously recorded.

Two years after the initial "attack" he began to improve. He was able to go on short vacation trips and moved to another city. A physical examination at that time showed a well-nourished, well-preserved man in no apparent pain or respiratory distress. Blood pressure was 120 mm. Hg systolic and 78 mm. diastolic, and the pulse rate 82 per minute. The heart was not enlarged by percussion and the heart sounds were normal. There was no physical evidence of cardiac insufficiency. A teleroentgenogram showed a heart shadow with a suggestion of enlargement of the left ventricle, the cardiothoracic ratio being 14/24. This, however, was explainable by his physical stature. An electrocardiogram was identical with that previously recorded.

In 1938, he became extremely nervous, lost weight and the pulse rate was said to average 100 per minute. No basal metabolic rate determination or electrocardiogram was done at the time but he took Lugol's solution for two months and improved greatly. Subsequent examination revealed no evidence of hyperthyroidism and no enlargement of the thyroid. There had been no recurrence of a similar condition.

Six months later, a routine electrocardiogram was unlike any of those previously obtained (figure 2). The P–R interval and QRS duration were now normal; small Q waves were present in Leads II and III, and T_2 and T_3 were inverted. Electrocardiograms taken during the following year were of variable patterns. Some with normal P–R interval had only a Q_3 with upright T_2 and T_3 (figure 3). At other times, complexes with both short P–R interval and normal P–R interval were found in the same tracing. At that time, no satisfactory explanation was apparent for these reversions from one to the other type of rhythm, which were spontaneous, but could not be induced by medication or carotid sinus stimulation.

The patient's general health continued to be good up to the time of our examination. There had been no changes in his physical examination and no signs of cardiac failure.

Comment

The manifestations in this case, on which the diagnosis of myocardial infarction were based, included a history of severe and protracted subpectoral pain and an electrocardiogram interpreted as showing bundle branch block. In 1940 the correctness of the original diagnosis was questioned. Continued observations over an eight year period did not confirm the serious implications of myocardial infarction and bundle branch block. Careful revaluation of all the evidence led to the belated conclusion that all the findings could be adequately explained by the Wolff-Parkinson-White syndrome in a patient with neurocirculatory asthenia on the following basis.

The patient with Wolff-Parkinson-White syndrome is prone to disturbances of cardiac rhythm, palpitation and cardiac awareness. These changes in rhythm may occur after exercise, due to paroxysmal tachycardia or numerous ectopic impulses. Such disturbances in rhythm may be accompanied by a sensation of precordial oppression, which may approximate a severe pain and a sensation of dyspnea in sensitive individuals.

This patient had a severe attack of precordial pain after a strenuous session of handball, but weakness and "wilting" were the outstanding symptoms. Palpi-

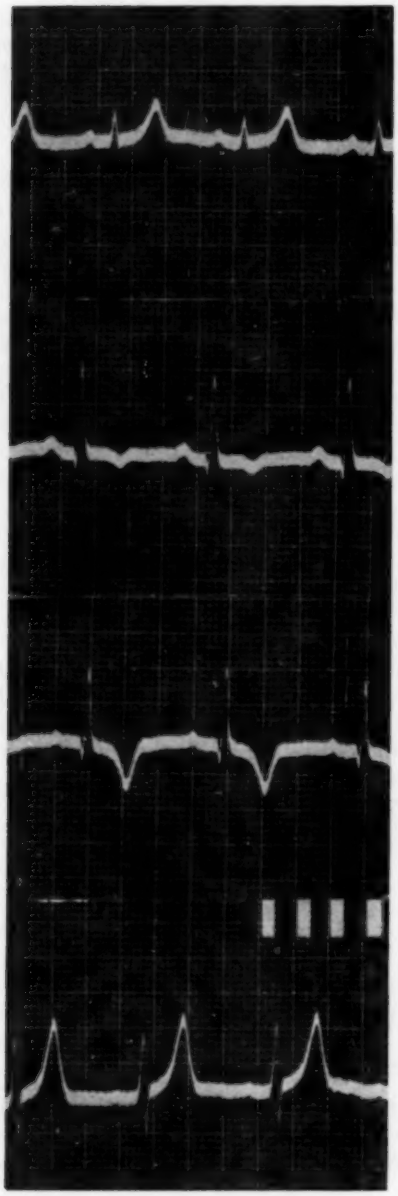

FIG. 2. Electrocardiogram, November, 1939, showing reversion to normal rhythm with P–R interval of .18 sec. and QRS duration of .08 sec. Note Q_2 and Q_3 and inverted T_2 and T_3, the changes which suggested posterior myocardial infarction.

tation was a prominent complaint and may have been due to paroxysmal rapid heart action.

Subsequent study failed to reveal evidence of organic heart disease, and revaluation of the clinical picture is consistent with neurocirculatory asthenia in a

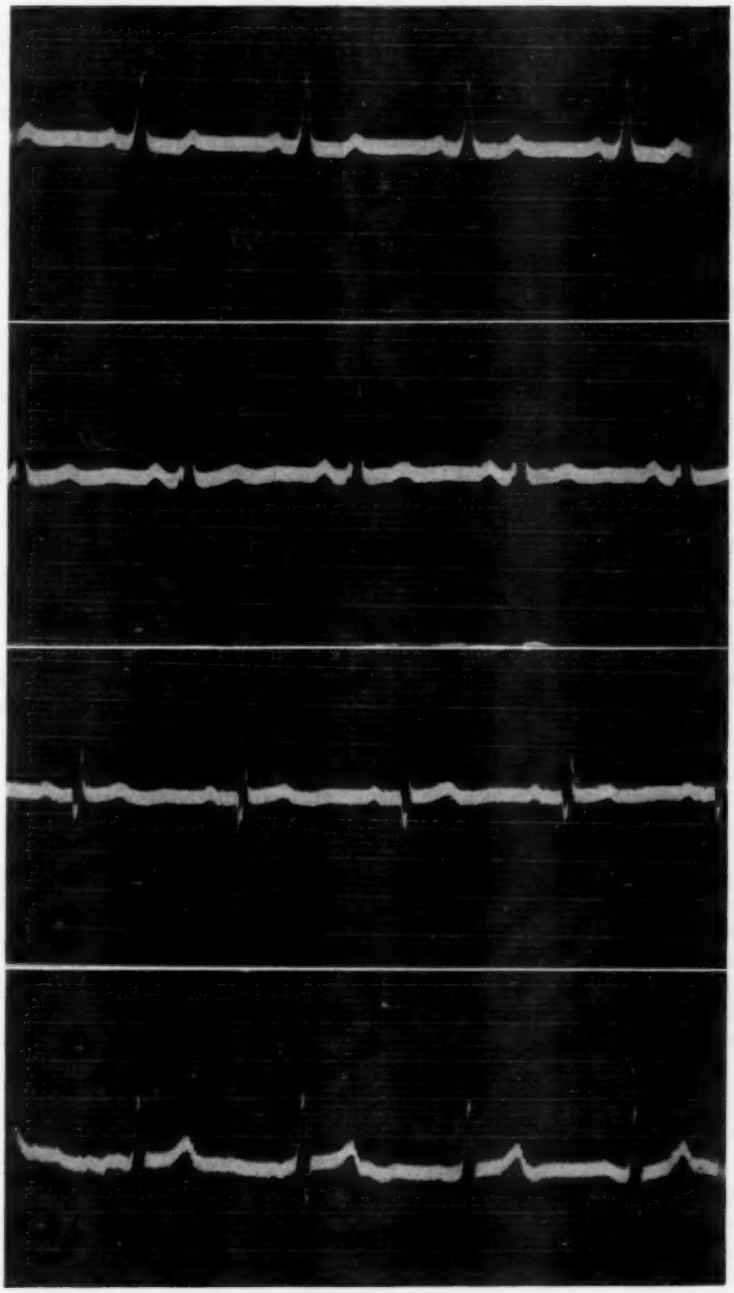

FIG. 3. Tracing showing normal rhythm. Note change in Q_2 and Q_3 and T_2 and T_3 compared to figure 2.

patient with the Wolff-Parkinson-White syndrome. Reassurance resulted in a significant amelioration of his symptoms.

It is known that the electrocardiograms of the Wolff-Parkinson-White syndrome may revert to a normal type spontaneously or in response to extracardiac stimuli or medication. In 1938 for the first time a tracing showed a normal P–R interval and normal QRS duration, but with a downward Q_2, T_2; Q_3, T_3 pattern. This suggested posterior myocardial infarction, which could however be excluded because these findings were inconstant (figure 3); furthermore, such unexplainable alterations in the electrocardiogram may occur in the Wolff-Parkinson-White syndrome.

Summary

1. A case is presented in which a diagnosis of myocardial infarction was made on a patient having a history of precordial pain and an abnormal electrocardiogram suggesting bundle branch block.

2. Later studies of this patient led to the conclusion that all of his symptoms and abnormal electrocardiographic changes were explained on the basis of the relatively benign Wolff-Parkinson-White syndrome in a patient with neurocirculatory asthenia.

3. It is important that all physicians interpreting electrocardiograms should be thoroughly familiar with the Wolff-Parkinson-White syndrome in order to avoid the error made in the case herein reported.

The author wishes to express his gratitude to Dr. Louis Wolff of the Beth Israel Hospital, Boston, Massachusetts, for his generous guidance in the preparation of this report.

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EDITORIAL

RATIONAL USE OF THE VITAMINS

WHEN, if, and how to take vitamins, what vitamins to take, whether to take pure vitamins or crude vitamin-complexes—these are only some of the questions that today must perplex the layman and indeed the physician as well, since the latter is called upon constantly to prescribe vitamins, interpret their effects, and above all to "debunk" vitamins. If we were to accept some of the more flowery claims for the vitamins that are glibly passed out to us over the radio, we might wonder how the human race ever managed to survive to see the dawn of the twentieth century with the advent of vitamins for all. And we should perhaps be astounded to learn that the great majority of human beings got along nobly in the olden days, even though they were not supplied with their daily vitamin requirement compactly assembled in a colorful little capsule. To put it mildly, the advertising claims for vitamins have been grossly exaggerated.

What then are vitamins and when are they indicated? Vitamins are not food nor even substitutes for food; they are not cure-alls nor do they provide energy, calories, or body-building materials. Vitamins may be defined as essential accessory food factors which act as catalytic agents aiding in the assimilation and utilization of foods in the body and playing all-important rôles in the metabolic processes of the body and the maintenance of various body tissues in a normal healthy condition. The body is incapable of synthesizing the majority of the vitamins (vitamin D being a notable exception), so that we must rely upon extrinsic sources of supply in the foods that we eat. Fortunately, the vitamins of proved importance in human nutrition are for the most part widely distributed in nature; hence, a well-balanced diet including meat, eggs, butter, milk, green and yellow vegetables, fresh fruits, and whole grain cereals should easily supply the daily vitamin requirement for the average healthy individual. Since no amount of vitamins is helpful without the essential foods, it is easy to understand why nutrition experts place the greatest stress on diet, emphasizing the need for eating the right foods in the right quantity. Experts declare that the average person who has been on a properly balanced diet has no business taking vitamin concentrates. The fact that the vitamins are non-toxic in the usual recommended doses is not sufficient justification for their indiscriminate use by healthy persons, even though this freedom of the vitamins from toxic side-effects is perhaps most fortunate in view of the ruthless manner in which commercial preparations are being foisted upon a gullible public.

At the present time seven vitamins, the chemical structures of which have been definitely established, are of proved importance in human nutrition, namely: (1) vitamin A or its precursor carotene, (2) vitamin B_1 (thiamin chloride), (3) vitamin B_2 (riboflavin), (4) nicotinic acid, (5) vitamin C

(ascorbic acid), (6) vitamin D (irradiated ergosterol), and (7) vitamin K (a naphthoquinone). In addition there is highly suggestive evidence that certain other recently identified vitamins of proved importance to lower animals are probably necessary for human nutrition as well. Among the latter are vitamin B_6 (pyridoxin), pantothenic acid, biotin, choline, and vitamin E (alpha tocopherol). It must be stressed that the actual function of these vitamins in human nutrition and the minimal human requirement are completely unknown. Nevertheless, small quantities of these chemicals have already been incorporated into a number of the current polyvitamin capsules in purely arbitrary dosage. On the other hand, there are undoubtedly a number of as yet unidentified vitamins important to human beings that can only be obtained by ingestion of the original food sources. This unknown factor furnishes one of the most potent arguments in favor of relying upon a well-balanced diet rather than commercial vitamin capsules for our daily vitamin intake.

When we encounter the full-blown clinical picture of beri-beri, pellagra, or scurvy, we do not hesitate to prescribe thiamin, nicotinic acid, or ascorbic acid respectively in massive doses with full knowledge that there is a deficiency of a specific known vitamin in each instance and that the administration of the missing factor will promptly alleviate the presenting symptoms. Equally well established are the indications for vitamin D in rickets and osteomalacia (with or without tetany), vitamin A in xerophthalmia and night-blindness, riboflavin in cheilosis and corneal vascularization, and vitamin K in the hemorrhagic diathesis associated with obstructive jaundice. In all instances, however, it is important to remember that, although the clinical manifestations may point largely to the deficiency of a single vitamin, a multiple deficiency frequently exists and the patient should be treated accordingly with a well balanced diet supplemented by the particular vitamin which is obviously lacking.

Far more difficult to recognize than the classical deficiency syndromes just mentioned are the vastly more numerous instances of subclinical deficiency, such as for example the pre-scorbutic or pre-pellagrous state. In this connection, the importance of an accurate dietary history cannot be too strongly emphasized, for it is only with the aid of such a history that the subclinical deficiency will be suspected. Conclusive proof of subclinical deficiency may then be obtained in certain cases by applying the various clinical methods of vitamin assay that have been worked out and by performing therapeutic tests. For example, let us consider subclinical thiamin deficiency. Anorexia, nausea, and nervous irritability have been shown to be early symptoms of thiamin deprivation, yet it would be pure folly—commercial advertisers notwithstanding—to conclude that all victims of these commonplace symptoms are suffering from thiamin deficiency or "B-complex deficiency." As a matter of fact, a good dietary history supplemented with urinary thiamin determinations would undoubtedly rule out a deficiency basis

in the great majority of patients with these complaints, and there would be no point in plying this majority with thiamin or other vitamins. On the other hand, the *temporary* administration of synthetic vitamins and crude vitamin complexes would seem to be justified in the treatment of individuals whose dietary habits had been so poor as to justify the suspicion of subclinical vitamin deficiency. The ultimate goal, of course, in treating such patients would be to educate them to the selection of a balanced diet in order that they might eventually discontinue the prescribed vitamin supplements.

So far we have shown little enthusiasm for vitamin therapy except in the relatively rare instances of outspoken deficiency. However, there are a number of conditions under which vitamin deficiency, either clinical or more often subclinical, is likely to develop. In many of these conditions, it may be impossible, impractical, or imprudent to treat the patient by adequate dietary measures alone; under these circumstances a real indication for supplements of synthetic vitamins and crude vitamin-complexes arises.

These abnormal conditions may be grouped under several broad headings: (1) *Decreased Intake of Vitamins* such as may occur in alcoholics who forget to eat, victims of gastrointestinal disorders such as ulcer or spastic colon where the patient may be afraid to eat because of pain, the edentulous and other patients on restricted diets (e.g. Sippy diet, reducing diets, elimination diets), post-operative patients, and febrile or psychiatric patients with anorexia. (2) *Impairment of Absorption* such as may occur in gastrointestinal disorders characterized by vomiting or diarrhea (e.g. pyloric obstruction, ulcerative colitis, fistulas), sprue with defective absorptive surface, reduction of absorptive surface (short-circuiting operations and intestinal resections), achlorhydria, obstructive jaundice (fat-soluble vitamins not well absorbed in the absence of bile salts), and excessive intestinal putrefaction. (3) *Increased Excretion* as in polyuria, diuresis, diarrhea, and lactation. (4) *Increased Requirement* as occurs in pregnancy and lactation, prolonged fevers, hyperthyroidism, diabetes (?), marked overactivity (e.g. manic psychosis or delirium), and excessively high carbohydrate diets. (5) *Impaired Utilization* as for example in hepatic disease and diabetes mellitus (?). Frequently a coexistence of two or more of the five conditions will be encountered in a single patient.

Granting that definite though limited indications for therapy with pure vitamins and vitamin complexes exist, we must next decide what constitutes a well balanced polyvitamin capsule. Such a capsule should contain at least the minimum normal daily adult requirement (as far as is known) of vitamins A, C, D, thiamin, riboflavin, and nicotinic acid: that is, vitamin A 4,000 U.S.P. units, vitamin D 400 U.S.P. units, thiamin hydrochloride 1 to 2 mg., riboflavin 2 mg., nicotinic acid (or the amide) 10 to 20 mg., ascorbic acid 30 to 50 mg. There is no need for the inclusion of vitamin K in such a capsule since the therapeutic indications for this vitamin are very specific and relatively rare. Furthermore, the addition of certain of the more recently

identified B-vitamins such as pyridoxine, pantothenic acid, and choline to such a capsule has little justification at the present while we are still completely in the dark as to the human requirement for these substances. When prescribing polyvitamin capsules, it is desirable to recommend a well balanced capsule such as has been described above. As a result of sales competition in an attempt to keep the price down, a number of very inferior capsules have been placed on the market. By skimping on certain of the more expensive ingredients, a firm can manufacture a relatively cheap capsule which may readily appeal to an unsuspecting public. The writer has found it expedient to note the riboflavin content of the various vitamin capsules in evaluating their relative merit; it is obvious that a capsule which contains "200 gammas" (200 micrograms or 0.2 milligram) of riboflavin is far inferior to one containing 2.0 milligrams of riboflavin, even though to the lay purchaser the figure "200" may appear the more impressive. In situations where supplementary vitamins are definitely indicated, it is well to prescribe in addition to a balanced capsule of pure vitamins some crude B-complex preparation such as yeast powder or crude extracts or concentrates of yeast, liver, or rice polishings in order to furnish the patient with important vitamins as yet unidentified. Vitamin-fortified white breads and cereals, though superior to the unfortified, are less nutritious than whole-grain breads and cereals.

On the basis of this discussion, we may now attempt to answer the questions posed in the opening paragraph. To the layman, we can say: if you are healthy, you should make a point of eating a well balanced diet and you will have no need for extra vitamins; if you are in ill health or obliged to follow a restricted diet for some special reason, choose your doctor rather than the radio for your guide as to what vitamin preparation you should take. And to the physician: educate your patients whenever possible to a well balanced diet and advise this group to forget about supplementary vitamins; in cases when additional vitamins are indicated, prescribe a well balanced polyvitamin capsule supplemented with some crude source of the B-complex; and by all means continue to "debunk" the vitamins to the world at large.

W. H. B.

REVIEWS

The Principles and Practice of Cardiology. By CRIGHTON BRAMWELL and JOHN T. KING. 509 pages; 25.5 × 16.5 cm. Oxford University Press, London. 1942.

This textbook follows a somewhat unusual plan for a book written on the subject of heart disease, in that it is divided into two parts, labelled "General Cardiology" and "Special Cardiology." Such a division is commonly seen in textbooks on pathology, but in this case the two parts are written by different authors.

The first section by the English author contains a number of rather surprising statements. In a discussion of heart failure the following statement is made about the association of auricular fibrillation with heart failure: "So frequent is this association that it is indeed difficult to collect a large series of congestive heart failure with normal rhythm."

In the section on treatment one finds the following: "Leeches, once so popular, are undoubtedly rarely used for therapeutic purposes. Nevertheless I have repeatedly obtained striking relief of pain due to hepatic congestion by the application of three or four leeches over the engorged liver." The use of cantharides is recommended in the treatment of acute pericarditis as a counter-irritant. The following statement is worth quoting in its entirety: "The ideal method of administering oxygen is to place the patient in an oxygen chamber. Unfortunately the cost of erecting such a chamber rules out this method except for research purposes. A modification of the oxygen chamber, namely, the oxygen tent as devised by the late Dr. E. P. Poulton, overcomes the financial embargo. I personally have used such a tent on two or three occasions with satisfactory results, but the difficulty of nursing the patient in the tent has prevented that method from gaining general popularity."

In the same section of "General Cardiology" the important subject of heart sounds is presented in confused fashion. Not only is the authors' terminology misleading, but he has completely overlooked the important contributions to the field made by North and South American investigators in the field of phonocardiography.

The section on "Special Cardiology" is somewhat better, but the important subject of rheumatic heart disease is presented in sketchy fashion, and the broader aspects of rheumatic fever as a long-term systemic disease are not included.

The limitations of space do not permit a cataloguing of even the most obvious deficiencies of this book. It adds nothing to the volume of literature which has already accumulated on the subject of heart disease. The text contains too many references to specific cases for a formal work on heart disease. This method of teaching is permissible in the clinic but is a serious drawback to an orderly presentation of the subject of heart disease.

C. W.

Synopsis of Diseases of the Heart and Arteries. Third Edition. By GEORGE R. HERRMANN, M.S., M.D., Ph.D., F.A.C.P., Professor of Medicine, University of Texas, Galveston. Third edition. 516 pages; 20 × 13 cm. C. V. Mosby Company, St. Louis. 1944. Price, $5.00.

A great deal of information has been crowded into the third edition of this volume. The material is divided into thirty-one chapters, of which a number might have been combined, to advantage, under more inclusive headings. The style is verbose and repetition is frequent. Many of the illustrations, particularly those picturing instruments and anatomical specimens, could have been omitted without loss. Some of the sketches are difficult to decipher because of much fine print and long legends.

The clinical descriptions are adequate and the therapeutic suggestions; for the most part, are sound. There is a tendency to list many forms of treatment, rather than to recommend one, or a few, of proved effectiveness in the hands of the author. Almost all of the electrocardiograms appear in the chapter devoted to the arrhythmias. Three figures depict the changes observed after cardiac infarction; none are shown in the sections on anginal heart failure (a poor term!), pericarditis or hypertension. Yet in the appendix are given new electrocardiographic data derived from the use of unipolar central terminal precordial leads.

In the chapter on military medicine the Schneider and 2-step tests for circulatory insufficiency, both of doubtful value, are unduly stressed. There is no bibliography but a number of articles are cited in the text. A few important references at the end of each chapter would be helpful to the serious reader.

Peripheral vascular diseases are covered in 40 pages. The author is clearly more interested and experienced in dealing with disorders of the heart. It hardly seems necessary to include formulas for the preparation of various solutions, such as physiological saline, Ringer's and isotonic glucose.

In the opinion of the reviewer, "synopses" such as this have no place in medical literature. The approach to knowledge cannot be both comprehensive and short. The busy practitioner or the student will find excellent, concise accounts of cardiovascular diseases in some of the standard text-books of medicine. Where more detailed information is desired on specific topics, he may consult special monographs, in which references to key papers also are given. In spite of the appearance of a third edition, this book is not recommended. Its subject matter is presented with equal brevity and greater clarity elsewhere.

R. L. L.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Global Epidemiology. A Geography of Disease and Sanitation. By JAMES STEVENS SIMMON, B.S., M.D., Ph.D., Dr. P.H., Sc.D. (Hon.), Brigadier General, A.U.S., TOM F. WHAYNE, A.B., M.D., Lt. Col., M.C., A.U.S., GAYLORD WEST ANDERSON, A.B., M.D., Dr. P.H., Lt. Col., M.C., A.U.S., HAROLD MACLACHLAN HORACK, B.S., M.D., Major, M.C., A.U.S., and Collaborators. Volume One: Part One—India and the Far East; Part Two—The Pacific Area. 504 pages; 26 × 18.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $7.00.

Malaria: Its Diagnosis, Treatment and Prophylaxis. By WILLIAM N. BISPHAM, Colonel, A.U.S., Retired. 197 pages; 23.5 × 16 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, $3.50.

The Blood Pressure and Its Disorders Including Angina Pectoris. By JOHN PLESCH, M.D. Budapest; M.D. Berlin; L.R.C.P. and S. Edin. and Glas.; Formerly Professor of Internal Medicine in the University of Berlin. 149 pages; 22 × 14.5 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, $4.50.

Vital Statistics and Public Health Work in the Tropics. By P. GRANVILLE EDGE, Lecturer in the Division of Epidemiology and Vital Statistics, London School of Hygiene and Tropical Medicine (University of London). Foreword by MAJOR GREENWOOD, D.Sc., F.R.C.P., F.R.S. 188 pages; 22 × 14.5 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, $5.00.

Diseases of the Digestive System. Second Edition. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P. 932 pages; 24 × 16 cm. 1944. Lea & Febiger, Philadelphia. Price, $11.00.

The Urinary Tract. A Handbook of Roentgen Diagnosis. By H. DABNEY KERR, M.D., and CARL L. GILLIES, M.D. 320 pages; 21 × 14.5 cm. 1944. The Year Book Publishers, Inc., Chicago. Price, $5.50.

Economy in the Use of Drugs in War-Time. Revised Second Edition. With an Appendix on Economy in the Use of Bactericides. Medical Research Council War Memorandum No. 3. 16 pages; 24.5 × 15.5 cm. 1944. His Majesty's Stationery Office, London. Price, $.10.

COLLEGE NEWS NOTES

Additional A.C.P. Members in the Armed Forces

Previously reported in the News Notes section of this journal were the names of 1,715 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,717:

Andrew M. Babey
C. P. Rhoads

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Book

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—"Simplified Diabetic Management," Fourth Edition.

Monograph

Dr. Richard D. Kepner, F.A.C.P., Honolulu, T. H.—"Mental Changes After Bilateral Prefrontal Lobotomy."

Reprints

Philip K. Arzt (Associate), Lieutenant, (MC), AUS—1 reprint.
Maurice Eliaser, Jr. (Associate), Major, (MC), AUS—1 reprint.
Dr. Abraham E. Jaffin, F.A.C.P., Jersey City, N. J.—1 reprint.
Dr. Josephine C. Lawney, F.A.C.P., New York, N. Y.—1 reprint.
Dr. D. O. N. Lindberg, F.A.C.P., Wabasha, Minn.—1 reprint.
Dr. Abraham M. Litvak, F.A.C.P., Brooklyn, N. Y.—2 reprints.
Dr. John H. Musser, F.A.C.P., New Orleans, La.—A group of 23 reprints by members of the faculty of Tulane University, many of whom are members of the College.
Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—2 reprints.
Dr. Aaron Parsonnet, F.A.C.P., Newark, N. J.—3 reprints.
Dr. Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—1 reprint.
Dr. Manuel de la Pila Iglesias, F.A.C.P., Ponce, Puerto Rico—1 reprint.
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—1 reprint.
Dr. Leon Schartz, F.A.C.P., Philadelphia, Pa.—1 reprint.
Dr. Maurice S. Segal, F.A.C.P., Boston, Mass.—1 reprint.
Dr. James F. Slowey (Associate), Cleveland, Ohio—1 reprint.
Dr. Frederick G. Speidel, F.A.C.P., Louisville, Ky.—1 reprint.
Dr. Frederick R. Taylor, F.A.C.P., Winston-Salem, N. C.—1 reprint.
Gilman R. Tyler (Associate), Major, (MC), AUS—1 reprint.
Dr. Michael Weingarten (Associate), New York, N. Y.—2 reprints.

New Life Members

The following physicians have recently become Life Members of the College through subscription to the permanent Endowment Fund of the American College of Physicians:

James Roderick Kitchell, F.A.C.P., Philadelphia, Pa.
Moise D. Levy, F.A.C.P., Houston, Tex.
T. C. Terrell, F.A.C.P., Fort Worth, Tex.

A.C.P. Regional Meetings

A combined Regional Meeting of the American College of Physicians for Idaho, Oregon, Washington, Alberta, British Columbia, Manitoba and Saskatchewan, and the War-Time Graduate Medical Meetings was held in Vancouver, B. C., September 14–15, under the chairmanship of Dr. George F. Strong, Regent. The scientific papers were of unusually high quality, and the most dramatic and perhaps most interesting event was the attendance of Commander C. M. Wassell, (MC), USNR, the internationally famous doctor whose gallant and heroic work President Roosevelt described in such glowing terms, and whose courage and devotion will never be forgotten in the annals of military medicine. There were in attendance 96 Service physicians from the United States and Canada, and 102 civilian physicians, or a total of 198 registered. Seven states of the United States and five Provinces of Canada were represented.

At Omaha, Nebr., October 23–27, the Omaha Mid-West Clinical Society held its annual meeting, which by arrangement with the American College of Physicians, the American College of Surgeons and the War-Time Graduate Medical Meetings, was a combined, coöperative effort. Members of the two Colleges and all medical officers in the state of Nebraska and neighboring States were invited to participate. On October 26, Dr. Malcolm T. MacEachern, F.A.C.P., Associate Director of the American College of Surgeons, spoke on "The American College of Surgeons' Program for the Expansion of Graduate Training in Surgery" and Mr. E. R. Loveland, Executive Secretary of the American College of Physicians, spoke on "The American College of Physicians—Its Aims, Standards and Activities."

A Regional Meeting for the territory embracing Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin was held at the Drake Hotel, Chicago, November 4, under the general chairmanship of Dr. Walter L. Palmer, Governor for Northern Illinois, and with the participation of the College Governors for the States represented. This Regional Meeting program also formed a part of the concluding day of the American College of Physicians' Postgraduate Course, Special Phases of Internal Medicine, held at the Northwestern University Medical School, October 23–November 4, under the directorship of Dr. Willard O. Thompson.

On November 11, at Pittsburgh, a Regional Meeting of the College for the states of Ohio, West Virginia and Western Pennsylvania was held at the William Penn Hotel, under the general chairmanship of Dr. R. R. Snowden, Governor for Western Pennsylvania, with the coöperation of Dr. A. B. Brower, Dayton, Governor for Ohio, Dr. Walter E. Vest, Huntington, Governor for West Virginia, and Dr. D. A. MacGregor, Wheeling, Deputy Governor for West Virginia.

Several regional meetings of the College are planned for the future, including one in Philadelphia on December 15, under the general chairmanship of Dr. Thomas M. McMillan, Acting Governor for Eastern Pennsylvania, for the territory embracing Eastern Pennsylvania, New Jersey and Delaware; one in Memphis, Tennessee, during January, under the general chairmanship of Dr. W. C. Chaney, Governor for Tennessee, and embracing the territory of Tennessee, Arkansas, Eastern Texas, Louisiana and Mississippi; one in Oklahoma City, February 22, 1945, under the general chairmanship of Dr. Lea A. Riely, Governor for Oklahoma, and embracing the states of Oklahoma, Western Texas, Kansas and Missouri.

A.C.P. Postgraduate Courses

The American College of Physicians conducted six postgraduate, refresher courses during the current autumn, beginning on October 2 and extending through December 15.

Course No. 1, Cardiology, at the Massachusetts General Hospital, Boston, under the direction of Dr. Paul D. White, was oversubscribed by more than four times its capacity of accommodations. There were in attendance 44 Fellows and 14 Associates, and 13 Non-members, making a total of 71. Of this number, 61 were civilian physicians and 10 were medical officers from the Armed Forces. Twenty-two States and the Dominion of Canada were represented. The largest number from any state was 12 from Pennsylvania.

With the exception of Course No. 2, General Medicine, at the University of Oregon, and Course No. 3, Special Phases of Internal Medicine, at the University of Minnesota, which had representative registrations, all courses were oversubscribed. The organization of these refresher courses has been characterized by many as one of the most important and valuable activities of the College.

Lt. Col. Charles H. A. Walton, F.A.C.P., retired from active duty in the Royal Canadian Army Medical Corps, September 7, 1944, and has returned to practice in Winnipeg, Manitoba.

Report from the Office of the Surgeon General, U. S. Army

General Fox Receives Typhus Commission Medal

Brigadier General Leon A. Fox, F.A.C.P., has been awarded the Typhus Commission Medal for "exceptionally meritorious service rendered first as Director and later as Field Director of the United States of America Typhus Commission." General Fox directed the Typhus Control Project of Naples in December, 1943, which brought the epidemic in southern Italy under control within a month.

General Simmons Receives Honorary Degree from Marquette

Brigadier General James S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Office of The Surgeon General, received the honorary degree of Doctor of Science and delivered the commencement address at the graduation exercises of the School of Medicine, Marquette University, Milwaukee, Wis., on September 27. Prior to the graduation, he addressed the Milwaukee Medical Society and the student body of Marquette Medical School on the subject of "Progress of the Army's Fight Against the Insects."

General Morgan Speaks on Penicillin

Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant of Medicine, Office of The Surgeon General, spoke on penicillin at a combined meeting of the Kentucky State Medical Association and the War-Time Graduate Medical Meetings at Lexington, Ky., September 19.

Communicable Diseases Figuring Prominently in the Present War

Meningococcal meningitis: As in the civilian population, this disease reached a prevalence several times higher than the normal inter-epidemic level in 1943; however, its prevalence has been somewhat lower than in the last war and its mortality, thanks to the sulfonamides, has been only a small fraction of that in the last war (case fatality rate 4.5% in 1943 as against 34.3% in 1917–1919).

Primary atypical pneumonia: Comparison with previous periods is impossible as this disease has only recently been recognized clinically. There is evidence that more of the pneumonias now occurring are primary atypical than of known bacterial etiology. The case fatality rate has been very low. The disease has had a seasonal distribution similar to that of the common respiratory diseases.

Diarrheal diseases: This group of diseases of diverse etiology, but having a common basis in deficiencies of sanitation, has shown a considerable increase from peacetime owing to the much greater number of troops on maneuvers, especially during the summer months, with the added problems of field sanitation. Case fatality is very low. The present trend of rates is downward.

With respect to other communicable diseases too, the record has been excellent. Measles, mumps and scarlet fever are reduced greatly, while diseases against which immunizing methods are practised (typhoid, smallpox, tetanus) have all but disappeared.

Recent Promotions

Lieutenant Colonel to Colonel

Irving Sherwood Wright, F.A.C.P., New York, N. Y.

Major to Lieutenant Colonel

Howard Phelps Lewis, F.A.C.P., Portland, Ore.

Walter L. Nalls, F.A.C.P., Richmond, Va.

Nutrition Consultants Appointed

Dr. Julian M. Ruffin, F.A.C.P., Associate Professor of Medicine, Duke University, Durham, N. C., and Dr. Virgil P. Sydenstricker, F.A.C.P., Professor of Medicine, University of Georgia, Augusta, Ga., have been appointed Consultants to the Surgeon General in the field of nutrition.

Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, and his associates, received the first award of merit for an exhibit on pituitary irradiation at the meeting of the American Roentgen Ray Society at Chicago recently.

Dr. William G. Leaman, Jr. F.A.C.P., Professor of Medicine at the Woman's Medical College of Pennsylvania, Philadelphia, has deposited in the files of the American College of Physicians a catalogue of the lantern slides collection of that Institution. There are 4,117 slides, both standard size ($3\frac{1}{4}'' \times 4''$) and small size ($2'' \times 2''$) in the collection of the Department of Medicine. Many of the small size films are Kodachrome. These slides are made available to any speaker on a College program in an emergency.

The Woman's Medical College of Pennsylvania is conducting its second annual postgraduate lecture course, given by the Department of Medicine, from September 27, 1944, through April 19, 1945. The classes meet from 7:00 to 9:00 p.m. This year's course will be devoted to clinical topics. Speakers have been chosen from the faculties of various medical schools in Philadelphia. The object of the course is to present to the general practitioner the recent advances in the field of internal medicine. Enrollment is limited to fifty and the fee for the entire year is $25.00.

Dr. L. B. Carruthers, F.A.C.P., Professor of Medicine and Dean of the Miraj Christian Medical School, Miraj, India, has recently been made a Member of the Royal College of Physicians of London.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, recently received the Decoration of the Heraldic Order El Sol Del Peru in the class of Knight Commander by His Excellency, the President of Peru. The citation reads:

> "As President of the San Francisco Chapter, Pan American Society, Dr. J. C. Geiger has aided materially in fostering and cementing friendly relations between countries of the Americas; as a teacher of preventive medicine and public health in universities, medical officer of health and chief of hospitals, he has added much to the glorious chapter of the prevention of disease."

Dr. Geiger made the commencement address at Tulane University School of Medicine on October 14, 1944, the largest commencement in the history of that University. Dr. Geiger was given the honorary degree of Doctor of Science, which was the second honorary degree to be conferred upon him by Tulane University. It is said that this is Dr. Geiger's fifth degree from Tulane and his seventh honorary degree from this and other universities.

Major Winthrop Wetherbee, Jr., F.A.C.P., was recently transferred from the Seventh General Hospital to the 116th General Hospital, overseas, as Chief of Medical Service.

Lt. Col. Joseph Hayman, F.A.C.P., has recently been placed in charge of a newly established special treatment center for malaria and other tropical diseases at the Moore General Hospital, Swannanoa, N. C.

On September 22, 1944, Dr. Herbert T. Kelly, F.A.C.P., Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, presented before the session on Nutrition of the Pennsylvnia Nutrition Council and State Council of Defense, at Harrisburg, Pa., a paper on "Conservation of Human Resources."

New Journal of Parenteral Therapy Established

Publication of a new quarterly, the Journal of Parenteral Therapy, has been announced by Science Publications Council, New York. The Advisory Editorial Board includes the following physicians and surgeons: W. Wayne Babcock, Philadelphia; I. A. Bigger, Richmond, Va.; Alexander W. Blain, Detroit; Frederick A. Coller, Ann Arbor, Mich.; Joseph H. Fobes, New York; Henry N. Harkins, Baltimore; Lester Hollander, Pittsburgh; Alton Ochsner, New Orleans; Max M. Strumia, F.A.C.P., Bryn Mawr, Pa.; George J. Thomas, Pittsburgh. Justus J. Schifferes, New York, is managing editor.

The Mississippi Valley Medical Society held its tenth annual meeting at Peoria, Ill., September 27–28. Among contributors to the program were: Dr. A. C. Ivy, F.A.C.P., Chicago, "The Rationale of Tests of Liver Function"; Dr. Willard O. Thompson, F.A.C.P., Chicago, "The Fröhlich Syndrome"; Dr. Edwin C. Ernst, F.A.C.P., St. Louis, "Diagnosis and Treatment of Cancer of the Cervix"; Dr. O. P. J. Falk, F.A.C.P., St. Louis, "Practical Points in Recognition and Management of Coronary Diseases"; Dr. R. O. Muether, F.A.C.P., St. Louis, "Round Table Discussion on Hypertension."

"Pathology of Internal Medicine" is the title of a postgraduate course scheduled at the Israel Zion Hospital, Brooklyn, which began on October 17, and will be conducted by Dr. Jacob M. Ravid (Associate), under the auspices of the Joint Committee on Postgraduate Education of the Long Island College of Medicine, the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn. The course is designed to familiarize the internist as well as the general practitioner with the fundamentals of gross and microscopic pathology of internal medicine. Great stress will be laid on gross pathological diagnosis of tissues and organs.

The International College of Surgeons, United States Chapter, was addressed at its Philadelphia National Assembly, October 3–5, by Dr. George Morris Piersol, F.A.C.P., Director of the Center for Research in Physical Medicine, University of Pennsylvania, on "Rehabilitation"; Dr. Charles M. Griffith, F.A.C.P., Washington, Medical Director of the Veterans Administration, spoke on "The Rehabilitation of Ex-Members of the Armed Forces by the Veterans Administration"; Dr. Truman G. Schnabel, F.A.C.P., Clinical Professor of Medicine at the University of Pennsylvania, spoke on "The Everpresent Post-Operative Respiratory Complications."

The New York Academy of Medicine conducts a Friday evening lecture series from November through April. On December 8, Dr. Emanuel Libman, F.A.C.P., will deliver an address on "Diagnostic Observations on Abdominal Diseases," and on January 12, Dr. H. McLeod Riggins, F.A.C.P., will deliver an address on "Present Trends in the Treatment of Pulmonary Tuberculosis."

Fellows of the College Serving as Chairmen of Sections, A.M.A.

Dr. William D. Stroud, F.A.C.P., Philadelphia, is serving as Chairman of the Section on the Practice of Medicine, and Dr. Louis H. Clerf, F.A.C.P., Philadelphia, is serving as Chairman of the Section on Laryngology, Otology and Rhinology, for the current year.

Dr. O. H. Perry Pepper, Captain Edward L. Bortz, (MC), USNR, and Dr. William D. Stroud, all of Philadelphia, are Fellows of the College who are among the foreign corresponding members of the Society of Internal Medicine of the Medical Association of Argentina.

Major General Charles R. Reynolds, F.A.C.P., U. S. Army retired, has resigned as Chief of the Division of Tuberculosis of the State Department of Health of Pennsylvania, to accept an appointment with the American College of Surgeons in Chicago. General Reynolds was Surgeon General of the U. S. Army from 1935–39.

Dr. Frank R. Menagh, F.A.C.P., and Dr. Clarence E. Reyner, F.A.C.P., both of Detroit, are President and Secretary-Treasurer, respectively, of the Detroit Dermatological Society.

Dr. Benjamin A. Shepard, F.A.C.P., because of ill health, has resigned as President of the Kalamazoo Tuberculosis Association.

Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn., addressed the Medical Society of Virginia at its annual meeting in Richmond, October 23–25, on "Penicillin."

Ernest L. Boylen, F.A.C.P., Major, (MC), AUS, formerly of Portland, Ore., has been awarded the Bronze Star for meritorious service in direct support of combat operations in Italy last December and January.

The Northwestern Ohio Medical Society observed its 100th anniversary at Findlay, Ohio, October 3. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., addressed the luncheon meeting on "Hints in the Recognition of Puzzling Abdominal Pain." Other speakers included the following members of the faculty of the University of Cincinnati College of Medicine: Dr. M. A. Blankenhorn, F.A.C.P., "The Toxic Reactions of the Newer Sulfonamides"; Dr. Leon Schiff, F.A.C.P., "Tests of Liver Functions in Health and in Disease."

Dr. John A. Toomey, F.A.C.P., Cleveland, was a guest speaker at the 55th annual meeting of the American Pediatrics Society, Atlantic City, September 26–27, his title being "Attempts to Isolate Poliomyelitis Virus in Fish."

The late Dr. Charles Hartwell Cocke, F.A.C.P., Asheville, provided in his will that his medical library, magazines and other publications be given to the Buncombe County Medical Society Library in Asheville. Dr. Cocke died on August 3.

Dr. Tom D. Spies, F.A.C.P., Birmingham and Cincinnati, was a guest speaker at the 79th annual session of the Michigan State Medical Society at Grand Rapids, September 27–29, his subject being, "Vitamins and the Practice of Medicine." Among military speakers on the program were Brigadier General Charles C. Hillman, F.A.C.P., "Tropical Medicine"; Colonel William C. Menninger, F.A.C.P., "Neuropsychiatry and the General Practitioner"; Brigadier Jonathan C. Meakins, F.A.C.P., Montreal, "What a Modern Army Health Service Should Be."

Colonel Neely C. Mashburn, F.A.C.P., has been appointed Surgeon at the AAF Training Command, Fort Worth, Tex.

Dr. Hugh H. Hussey, Jr., F.A.C.P., has been named Chairman and Dr. Roy L. Sexton, F.A.C.P., has been named a member of a medical advisory committee appointed by the District of Columbia Office of Price Administration to pass on all applications for extra food rations for convalescents and persons in ill health.

Dr. Thomas N. Hunnicutt, Jr., F.A.C.P., Newport News, Va., has been elected President of the Warwick County Medical Society.

Dr. Alfred Meyer, F.A.C.P., New York City, is probably the oldest physician among Fellows of the American College of Physicians; aged 90, born in 1854. Although now retired, Dr. Meyer keeps up an active interest in medicine. He received his B.A. from Columbia University in 1874 and his Medical Degree from the College of Physicians and Surgeons, Columbia University, in 1877. He did extend postgraduate study at the University of Leipsic, at the University of Vienna and in hospitals of London, Paris and Rome. He has had a distinguished career, has published many contributions to the literature, and has been a Fellow of the American College of Physicians since 1919.

War-Time Graduate Medical Meetings

Region No. 1 (Maine, New Hampshire, Vermont, Massachusetts) and Region No. 2 (Connecticut, Rhode Island)—New England Committee for War-Time Graduate Medical Meetings—Dr. W. R. Ohler, Chairman; Dr. L. E. Parkins, Secretary.

Station Hospital, Dow Field, Bangor, Maine

December 21 Head, Spine and Nerve Injuries

Dispensary, U. S. Naval Air Station, Brunswick, Maine

December 21 Burns and Reconstruction Surgery

Station Hospital, Fort Williams, Portland, Maine

December 21 The Skin

Station Hospital, Presque Isle, Maine

December 21 Stomach, Biliary Tract, Intestinal Disorders

Dispensary, U. S. Naval Construction Training Center, Quoddy Village, Maine

December 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum

Station Hospital, Grenier Field, Manchester, New Hampshire

December 20 Peripheral Vascular Disease

U. S. Naval Hospital, Portsmouth, New Hampshire

December 21 Diarrheal Diseases

Boston Area Station Hospital, Waltham, Massachusetts

December 21 The Use of Penicillin and the Sulfa Drugs

U. S. Naval Hospital, Chelsea, Massachusetts

December 21 Blood Dyscrasias and Transfusions

Lovell General Hospital, Fort Devens, Massachusetts

December 21 The Pneumonias and Other Respiratory Infections

Station Hospital, Camp Edwards, Massachusetts

December 21 The Psychoneuroses and Their Management

Cushing General Hospital, Framingham, Massachusetts

December 21 Contagious Diseases and Complications

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

December 21 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

U. S. Marine Hospital, Brighton, Massachusetts

December 21 Acute Infections of the Central Nervous System

Station Hospital, Westover Field, Chicopee Falls, Massachusetts or U. S. Naval Convalescent Hospital, Springfield, Massachusetts

December 21 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island

December 21 Joint Injuries

U. S. Naval Hospital, Newport, Rhode Island

December 21 Fractures of Extremities

Station Hospital, Bradley Field, Windsor Locks, Connecticut

December 21 Fractures of Extremities

Air Corps Station Hospital, New Haven, Connecticut

December 21 Chest and Abdominal Injuries

Station Hospital, Fort H. G. Wright, Fishers Island, New York

December 21 Acute Abdominal Emergencies

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

Station Hospital, Camp McCoy, Wisconsin

November 29 Endocrinology
a. Addison's Disease
b. Adrenal Cortex in Shock
c. Parathyroid Tetany
d. Traumatic Hypogonadism
e. Hypothyroidism
f. Hyperthyroidism
g. Post Traumatic Pituitary Syndrosis
—Dr. Elmer L. Sevringhaus

December 13 Virus and Rickettsial Diseases
a. Virus Diseases
b. Rickettsial Diseases
—Dr. Marcos Fernan-Nunez

Station Hospital, Truax Field, Wisconsin

November 29 Gall Bladder and Liver Disease
a. Mechanism of Liver Function
Diagnosis and Medical Treatment of Liver and Gall Bladder Disease
b. Surgical Pathology and Treatment
—Dr. E. R. Schmidt

December 13 Thrombosis, Thrombophlebitis and Anticoagulants
a. Thrombosis, Thrombophlebitis and Embolism
Diagnosis and Treatment
b. Heparin and Dicoumarol
Action and Therapeutic Use
—Dr. Armand J. Quick

Note: War-Time Graduate Medical Meetings at Camp McCoy and Truax Field are arranged by the coöperating committee for Wisconsin. The members of this committee are Dr. Erwin R. Schmidt, Chairman; Dr. Elmer Sevringhaus and Dr. Francis D. Murphy.

Directory of Medical Specialists

The biographic data of the first two editions of the Directory of Medical Specialists included only positions (internships, residencies, or assistantships) held during the course of training of men up to the time of their certification by the American Boards, and hospital and medical school staff positions then currently held.

It is desired to extend these data in the Third Edition to include all formal hospital and medical school appointments, with dates held, even though now resigned, as well as records of all military service including commissions and dates, either in World War I, peace-time in the Reserve forces, or in the present war.

Thus, a chronologically complete sketch of a Diplomate's entire career is to be included in this Third Edition of the Directory.

Membership or fellowship in national or sectional (not local) special societies, and national general societies with offices held, and dates, in any of these, should be reported.

Membership in recognized international medical societies may be included, but honorary or other membership in foreign medical societies should not be reported.

Reference to the Second Edition (1942) of the Directory may be made for lists of medical societies to be included in one's biographic sketch.

Families or secretaries of men absent in military service are asked to complete or correct previous listings on new forms now being mailed to those eligible for inclusion in the Directory. Only those certified by an official American Board can be included, and there is no charge for this listing.

The foregoing notice is published in response to many inquiries, to assist those certified by the American Boards who are now engaged in correcting their previous listings, or preparing new sketches for the Third Edition of the Directory to be published early in 1945.

Communications should be addressed to the Directory of Medical Specialists, 919 North Michigan Avenue, Chicago 11, Illinois.

Dr. Walter A. Bastedo has called attention to an error occurring on page 507, Annals of Internal Medicine, September, 1944. He writes: "The New York Academy of Medicine Committee on Drug Exhibits is composed of Drs. Arthur DeGraff, Cary Eggleston, Harry Gold, Charles C. Lieb and George Wallace, with the writer (Walter A. Bastedo) as Chairman. This Committee has as its object the maintenance of a continuous exhibit of the newer remedies, which shall be scientific, educational and non-Commercial.

"As an auxiliary to this Committee an Advisory Committee of Drug Manufacturers was formed with Dr. Theodore G. Klumpp as Chairman."

OBITUARIES

DR. JOHN THOMAS MURPHY

Dr. John Thomas Murphy, F.A.C.P., died on the 15th day of June, 1944, at the age of 58. He had just completed his thirty-eighth year of medical practice, having graduated in medicine at the early age of 21.

He received his degree of Doctor of Medicine from the University of Toledo in 1906. In 1907 he was instructor in Histology in this university and during the following two years, 1908–09, an instructor in Pathology. His interest in these fields persisted throughout his life.

Through the hobby of photography he was led into his chosen field of roentgenology. His early training in this new specialty was obtained in Cook County Hospital in Chicago. He was appointed to the directorship of the Radiological Department of St. Vincent's Hospital in Toledo in 1917, a position which he held until his death.

In medicine, as in all of his interests, his prime motive was to determine the basic facts. It was this constant search for the truth, with a total abhorrence of half truths, that made him an outstanding man in whatever he undertook and placed him among the leaders of roentgenology.

In play, as in work, John Murphy expended his full energy. As a boy and young man he excelled in athletics, especially track. Ice skating was a hobby which held his interest throughout life. His experiences in early flying were always a source of satisfaction to him and later stimulated him to take an interest in other young men who were similarly inclined. Thus came the inspiration to start, along with other Toledo persons, the Civil Air Reserve.

To few men are given the qualities of attraction and endearment which Dr. Murphy possessed. Many honors were bestowed upon him, yet he remained modest and unaffected.

Dr. Murphy was a member and past president of the Academy of Medicine of Toledo and Lucas County; member of the Ohio State Medical Association; member of the American Medical Association and secretary of its Radiological Section from 1931 until his death; past president of the Detroit Roentgen Ray Society; charter member of the Ohio State Radiological Society; secretary of the American Roentgen Ray Society, 1928–31, president 1934; member of the American Radium Society; member of the Radiological Society of North America; president of the American College of Radiology in 1935; fellow of the American College of Physicians.

With the passing of this man organized medicine has lost an energetic champion, the community a faithful citizen, his friends and associates a wise and sympathetic counsellor, his family a generous and devoted father and his patients a good physician.

C. E. HUFFORD, M.D., F.A.C.P.,
Toledo, Ohio

DR. GROESBECK FRANCIS WALSH

Dr. Groesbeck Francis Walsh, (F.A.C.P.), Fairfield, Alabama, died September 1, 1944, of carcinoma of the urinary bladder. Dr. Walsh, who had been a Fellow of the College since 1931, was born in Chicago, Illinois, March 31, 1878. He received his A.B. degree in 1898 from St. Ignatius College (now Loyola University, Chicago) and his M.D. from Northwestern University Medical School in 1902. He was engaged in postgraduate study at Leland Stanford University in 1912 and 1913. He was First Assistant, Surgical Clinic, Colon Hospital, Canal Zone, 1907–10; Health Officer, Republic of Nicaragua, 1908; and Chief of Surgical Staff, Candelaria Hospital, Amazonas, Brazil, 1910–11. In 1919 Dr. Walsh became Chief of Medical Clinic, Employees' Hospital of the Tennessee Coal, Iron and Railroad Company, and remained in that position until his death. He was a member of the American Public Health Association, American Trudeau Society, American Association of Industrial Physicians and Surgeons, American Association for the Advancement of Science, Alabama Academy of Science, Jefferson County Medical Society, Alabama State Medical Association, Southern Medical Association, and Birmingham Clinical Club; Fellow, American Medical Association. He was former President (1932–34) of the Southern Interurban Clinical Club and Diplomate of the American Board of Internal Medicine. Dr. Walsh served in World War I as Chief of Laboratory Division, Naval Operating Base, Hampton Roads, Virginia, and in the Transport Service, U.S.S. Orizaba.

Dr. Walsh was a keen clinician and was much interested in the psychosomatic side of medical practice. In recent years the subject of handedness intrigued him greatly and he delved deeply into both lay and medical literature in research along this line, finding in Shakespeare particularly many references to left handedness. He was the author of many published papers. Dr. Walsh was a great lover of flowers, with a wide knowledge of horticulture. He was a wise counsellor, most attractive personally and greatly beloved by many friends. He will be sadly missed in the medical profession of Alabama.

FRED W. WILKERSON, M.D., F.A.C.P.,
Governor for Alabama

DR. ANDREW PORTER BIDDLE

Dr. Andrew Porter Biddle, F.A.C.P., was born in Detroit, February 25, 1862, and died in the city of his birth August 2, 1944, at the age of 82.

His primary and secondary education in the public schools of Grosse Ile and Detroit was supplemented by special studies in Geneva, Switzerland, Heidelberg, and Leipzig, Germany. He received an appointment as cadet and entered the United States Naval Academy in 1880, but later had to withdraw because of a visual impairment. He then entered the Detroit College of Medicine where he received the degree of Doctor of Medicine in 1886.

Dr. Biddle's services to his profession, and to the community in which he lived were legion. Space permits mention here of only a few of the more outstanding: Professor of Dermatology at his Alma Mater; Consultant, St. Mary's, St. Joseph's Mercy, Children's, and Woman's Hospitals, and Detroit Board of Health; First President, Detroit Dermatological Society, 1922, and President of American Dermatological Association, 1925–26; Formerly Secretary, Councillor and President of the Michigan State Medical Society, the only member ever to be honored with two successive terms as President during the eighty years of the Society's existence; Co-organizer and first Editor of the Journal of the Michigan State Medical Society, a position which he held for four years; former Secretary of Wayne County Medical Society; for many years member of the Detroit Library Commission and of the Detroit Board of Education, becoming President of this body.

In recognition of these splendid services and of Dr. Biddle's sterling worth as a man the following honors have been bestowed upon him: Doctor of Science, honorary, College of the City of Detroit, 1929; Master of Science, honorary, University of Michigan, 1935; Andrew P. Biddle oration established by the Michigan State Medical Society. Fitting resolutions of eulogy were passed by Michigan State Medical Society and Wayne County Medical Society and made a part of the permanent records of those societies.

Industrious and frugal during his long life, Dr. Biddle was able to make several bequests. Chief among these were bequests to Michigan State Medical Society, to the University of Michigan, and to the Detroit Library Commission. These were all made in the interest of postgraduate education, a matter that was close to his heart.

The Michigan Fellows and Associates of the American College of Physicians join his other friends in mourning the passing of a great man.

P. L. Ledwidge, M.D., F.A.C.P.,
Acting Governor for Michigan

DR. JOSEPH P. TRAYNOR

Dr. Joseph P. Traynor of Natick, Mass., died September 12, 1944. He was born at Biddeford, Maine, in 1878, graduated in medicine from Bowdoin Medical School in 1901, and early in his career entered the Medical Corps of the United States Navy. During his career as a Naval Medical Officer, his assignments covered most of the important stations in the world from which the Navy operates. He did postgraduate work at the Naval Medical School and at the Massachusetts General Hospital.

Some years ago he retired from active duty and has, in the meantime, resided at Natick, Mass.

He had been a Fellow of the American College of Physicians since 1923.

DR. JOSEPH LESLIE SHERRICK

The death of Dr. Joseph Leslie Sherrick, F.A.C.P., of Monmouth, Illinois, on July 28, 1944, is a deep loss to the community he served and to the medical profession. His thirty years of fine medical service, the wide scope of his interests, the esteem in which he and his ability were held, mark him as one who typified the ideals of The American College of Physicians. The generous living of such a man as Dr. Sherrick is one of our strongest arguments against socialized medicine.

Dr. Joseph Leslie Sherrick was born in Little York, Illinois, in 1888. He received his A.B. from Monmouth College in 1908, and his M.A. from Yale in 1910. He attended the Johns Hopkins University School of Medicine in 1914, and interned at Massachusetts General Hospital in 1914–1915. He was for many years a Member of the Staff of the Monmouth Hospital; a Trustee of Monmouth College; Associate Medical Director of the Illinois Bankers Life Assurance Company; Director of the Second National Bank of Monmouth; Member of The Warren County Medical Society; Member of the Illinois State Medical Society; Fellow of The American Medical Association, and Fellow of The American College of Physicians since 1926. He died July 28, 1944, at the age of 56.

Dr. Sherrick was physician for the C. B. & Q., and the M. & St. Louis Railroads. He was resident physician for Monmouth College for Women, and for the past year and a half has been civilian physician for the Naval Flight Preparatory School at the College. He has served as Internist on the Medical Advisory Board No. 16 of the Selective Service for the past three years. He was a member of Monmouth Lodge No. 37 A.F. and A.M. and of the First United Presbyterian Church. He was Secretary of the Monmouth Medical Club for twenty years, also Secretary of The Monmouth Hospital Staff for the same number of years.

Dr. Sherrick's father was a physician in Monmouth and died two years after his son joined him in practise there. Their combined service to the community extend over almost fifty years. He is survived by his wife and two sons, First Lieut. Joseph C. Sherrick, M.D., now stationed at Carlisle Barracks, Pa., and John M. Sherrick, a chemist in Chicago, Illinois.

His death followed an attack of acute respiratory disease which had confined him to his bed for several weeks. Our untimely loss of Dr. Sherrick when he was in the midst of all his valuable services can be recorded as another war casualty.

CECIL M. JACK, M.D., F.A.C.P.,
Governor Southern Illinois

DR. FOSTER LEONARD DENNIS

Dr. Foster Leonard Dennis, F.A.C.P., Dodge City, Kansas, was born in Potawatomie County, Kansas, November 12, 1895. He attended the

University of Kansas for three years, and then transferred to St. Louis University, from which he received his B.S. degree in 1918. He graduated in medicine from the Jefferson Medical College of Philadelphia in 1921, and thereafter spent a two-year internship at St. Mary's Hospital in Kansas City, Mo. At one time, he served as Director of the Clinical Laboratory and Instructor in Medicine and Bacteriology to the Nurses Training School, St. Anthony's Hospital, and was Chief of Staff there from 1932 to 1934. He was also Physician-in-Chief, Kansas State Soldiers' Home Hospital. Dr. Dennis was commissioned a Major in the Medical Corps, Army of United States, on February 24, 1943 and for a time was stationed at the Walter Reed General Hospital in Washington, D. C., and thereafter attached to the 22nd General Hospital.

Dr. Dennis was a member of the Kappa Sigma and Phi Chi Fraternities, and of Illustriana, a society of professional men, native born Kansans. He was a member of the Ford County Medical Society and the Kansas State Medical Society, was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1929. He died June 26, 1944, of cerebral hemorrhage, at the age of 48. Possessed of a charming and pleasing personality, he was interested in scientific medicine, was a progressive and intelligent man, highly regarded by his fellow practitioners.

DR. FRANKLIN DAVIS WILSON

Dr. Franklin Davis Wilson died November 17, 1943, in Norfolk, Virginia, after many years of hard work. Dr. Wilson was born in Norfolk County, Virginia, June 8, 1882. He received the degree of Doctor of Medicine from the University of Maryland School of Medicine and College of Physicians and Surgeons in 1908. Following this, he returned to South Norfolk where he practiced until 1918 when he went to Harvard for a year and a half post-graduate study of Pediatrics. Following this period, Dr. Wilson returned to Norfolk and took up his work in the field of Pediatrics to which he contributed in many ways. Prior to graduation, Dr. Wilson had been Clinical Assistant at the University of Maryland Hospital from 1907–1908, and later, following specialization in Boston, he became a House Officer in the Children's Hospital in Boston from 1909–1920.

A long list of appointments in this field attest his service to his fellow man. Dr. Wilson was Consultant in Pediatrics at Mt. Sinai and Norfolk Memorial Hospital. Lecturer in Pediatrics at the Nurses Training School, Norfolk Protestant Hospital, Vice-President and Visiting Physician, Bonney Home for Girls; formerly, Visiting Physician, King's Daughters Children's Hospital; member of the Norfolk County Board of Health, 1916–1918; formerly member of the Norfolk Council of Social Agencies and of the Norfolk County School Board; formerly President and Visiting Physician of

the Norfolk Society for the Prevention of Cruelty to Children. He was the author of numerous publications dealing with Child Health and Welfare.

In addition to these appointments, he was former President of the Norfolk County Medical Society and the Virginia Pediatric Society; also member of the Medical Society of Virginia, American Academy of Pediatrics, the Southern Medical Association, American Medical Association, Tri-State Medical Society of Carolina and Virginia, and the Seaboard Medical Society, as well as a Fellow of the American College of Physicians since 1931.

Dr. Wilson was a man of deep religious convictions and a member of the Society of Friends. His quiet, determined efforts were devoted largely to the problems of children and child welfare. His efforts in the field of children's work were not limited to the Norfolk area as he served on the Child Welfare Committee of the State of Virginia since 1933, having been Chairman since 1936. He leaves his wife, a son, and two daughters.

J. Edwin Wood, Jr., M.D., F.A.C.P.,
Governor for Virginia

DR. ROBERT L. CUNNINGHAM

Dr. Robert L. Cunningham, F.A.C.P., Los Angeles, Calif., died suddenly at his home on September 10, from his second attack of coronary thrombosis. The first attack occurred more than 10 years ago.

Dr. Cunningham was born at Shushan, New York, in 1880. His school days were spent in Indiana, and he obtained his A.B. degree at Wabash College in 1901. He received his medical training at Johns Hopkins University School of Medicine, graduating in 1907 and remaining there as interne the following year. He went west after completing his interneship and began to practise as an internist in Los Angeles, California, devoting himself especially to the study of diseases of the lung. He became a well-known figure at the Barlow Sanitarium as attending physician from 1911 until the time of his death. He became, successively, President of the Los Angeles Tuberculosis Association from 1930–1933 and of the California Tuberculosis Association in 1934. For many years he was Clinical Professor of Medicine at the University of Southern California School of Medicine, member of the staff of the Hospital of the Good Samaritan, and consulting physician at the Children's Hospital and St. Vincent's Hospital.

Dr. Cunningham was a past president of the Los Angeles Academy of Medicine, a member of the Los Angeles County Medical Society, the California State Medical Association, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1927. His death means a great loss to his friends and the entire medical profession of Southern California.

Roy E. Thomas, M.D., F.A.C.P.,
Governor for Southern California

DR. MALCOLM GRAEME MacNEVIN

Dr. Malcolm Graeme MacNevin, F.A.C.P., San Francisco, Calif., died on a train May 21, 1944, of chronic myocarditis and coronary occlusion; aged, 78. He was born at Caledonia, Ontario, on November 23, 1865, attended the local public schools and prepared under private tutor for admission to the University of Michigan, from which he received his M.D. degree in 1890. He chose the United States for his permanent home and became a naturalized citizen. For twelve years, 1894 to 1906, he was Chief Surgeon, St. James Hospital, Butte, Mont. However, he became interested in gastro-enterology and problems of nutrition, and made these his special field of endeavor for the balance of his life.

Dr. MacNevin did postgraduate work at Guys Hospital and the London Hospital of England, and at the University of Berlin in Germany. Between his work in Butte, Mont., and his going to San Francisco, he spent a considerable period of time in New York City, where he was Assistant Professor of Medicine and Chief of the Medical Clinic at the New York Post Graduate Medical School and Hospital; also Attending Physician at St. Barnabas Hospital and Consulting Gastro-enterologist at the Hospital for Ruptured and Crippled. In 1931 he became attached to the Southern Pacific Hospital at San Francisco, which appointment he held to the time of his death. He had been a Fellow of the American College of Physicians since 1929.

DR. FRANCIS PATRICK McNAMARA

Dr. Francis Patrick McNamara, F.A.C.P., Dubuque, Iowa, died July 2, 1944, aged 59. He was born at Fitchburg, Mass., December 22, 1884. He graduated from Harvard Medical School in 1918, and thereafter did postgraduate work in Pathology and Bacteriology at Yale University, and Biochemistry at Harvard.

He early restricted his work to the field of Pathology. He was at one time Assistant in Bacteriology, Assistant in Pathology and Instructor in Pathology at Yale University Medical School. Since 1922, he had been Pathologist at the Finley Hospital, Dubuque; Consulting Pathologist at Decorah Hospital; member of the staff, St. Joseph Mercy Hospital. Dr. McNamara was a member of the Iowa State Board of Health and served as President of the Iowa State Medical Society, 1940–41. He had also been President of the Dubuque County Medical Society. He was a Fellow of the American Medical Association, and in 1933 received its Silver Medal for a scientific exhibit illustrating the activities of the pathologic laboratory in a hundred-bed hospital. He was also a member of the American Association of Pathologists and Bacteriologists, American Society of Clinical Pathologists and the American Society for the Control of Cancer. He was a Diplomate of the American Board of Pathology, and had been a Fellow of the American College of Physicians since 1931.